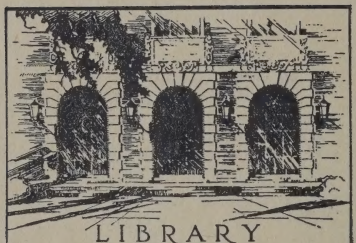
TOXOPLASMOSIS

by

Dr C. D. BINKHORST

STENFERT KROESE · LEIDEN



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TOXOPLASMOSIS

TOXOPLASMOSIS

A CLINICAL, SEROLOGICAL AND HISTOPATHOLOGICAL STUDY WITH SPECIAL REFERENCE TO THE EYE MANIFESTATIONS

Presentation of Twenty Cases of Proved or Presumable Toxoplasmic Retinopathy and Retino-encephalopathy with Associated Ocular Manifestations

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Dr C. D. BINKHORST

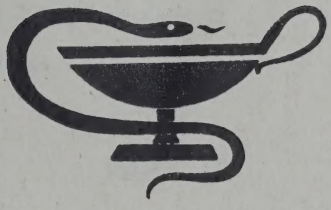

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Fig. 1: Geographical distribution of reported cases of toxoplasma in human tissues.

Fig. 1: GEOGRAPHICAL DISTRIBUTION OF REPORTED CASES OF TOXOPLASMA IN HUMAN TISSUES

New-York : Wolf and Cowen (1) ; Wolf, Cowen and Paige (1, 5, 6) ; Plaut

Chicago : Richter

Boston : Hertig

Detroit : Zullzer ; Steiner and Kaump

Minneapolis : Adams

St. Louis : Callahan c.s. ; Pinkerton and Henderson

Charleston : Pratt-Thomas and Cannon

Cincinnati : Sabin (2) ; Steiner and Kaump

Rochester : Syverton and Slavin

Philadelphia : Winkelman and Moore

Panama : Kean and Grocott (1, 2) ; Tomlinson

Lima (Peru) : Pinkerton and Weinman

Rio de Janeiro : Torres ; Guimaraes

Amsterdam : de Lange (1, 2)

Groningen : Vos ; Dekking

Rotterdam : Davel c.s. ; Ziedses des Plantes

Paris : Lelong

Genève : Bamatter (2, 3)

Basel : Freudenberg ; Müller (Bamatter (3))

Zürich : Gasser and Schwarz

Italy : Robinson

Corsica : Coulon

Prague : Jankû

Norway : Boesen

Stockholm : Magnusson and Wahlgren

INTRODUCTION

After the discovery of toxoplasma-like protozoa (LAVERAN (1900)) many years passed, in which similar protozoa were exclusively observed in animals. In 1923, however, the Prague ophthalmologist JANKÛ found protozoa in the eye of a hydrocephalic infant, that had died at the age of 11 months. Little attention was paid to JANKÛ's statement which is presumably to a very large extent to be attributed to the fact that the publication only appeared in Bohemian.

It is now pretty well certain that the protozoa observed by JANKÛ were toxoplasmas.

Only in 1939 did the occurrence of toxoplasma as a cause of disease in man become an established fact by the Americans WOLF, COWEN and PAIGE (3) isolating protozoa from the brain of a child that died at the age of 31 days and demonstrating conclusively the morphological, biological and immunological identity of the protozoa with toxoplasma. WOLF, COWEN and PAIGE as well as SABIN have rendered signal service by their fundamental work on human toxoplasmosis.

Cases of human toxoplasmosis have been reported from North and South America and from many countries of Europe. The total number of reports on toxoplasma in human tissues exceeds 49. In a few cases, the presence of toxoplasma in body fluids has been more or less convincingly defended on the ground of animal inoculation experiments, while a great number of cases have been diagnosed by the demonstration of specific anti-bodies in the blood-serum.

The mode of infection in man is only partially known. In a number of cases it is a fact that the child has been prenatally infected by the mother. JANKÛ has already pointed out the prenatal origin of the symptoms in his case. WOLF, COWEN and PAIGE (4) have devoted a separate article to the congenital character of many cases of toxoplasmosis. They bring forward as a proof the symptoms observed prior to or just after birth (such as : hydrocephalia in utero, inactive fundus lesions shortly after birth, microphthalmia), and the presence of specific toxoplasma neutralizing anti-bodies in the blood of the mothers of the children. These observations have been repeatedly

confirmed since then by others. In other cases one can only presume whether the infection has been acquired prenatally or post-natally.

The incubation-period of toxoplasmic infection in man is unknown. By analogy of animal experiments, however, it is likely that the incubation-period, dependent on the infecting dose and the virulence of the toxoplasma, as well as on the adaptation of the toxoplasma to the host, may vary very considerably. It seems that the infection may remain clinically inapparent for a long, even for an indefinite time.

The existance of asymptomatic toxoplasmosis in man was very early suspected. The mothers of children with congenital toxoplasmosis in many cases reveal no symptoms. The prenatal origin of the infection in the child, as well as the demonstration of maternal neutralizing anti-bodies led, however, to the conviction that the mothers were infected or still harboured a latent infection, which was transmitted to their off-spring in utero.

Investigations carried out by SABIN (4) and later by CALLAHAN and HEIDELMAN confirm the impression that asymptomatic toxoplasmosis in rather wide-spread. SABIN estimates that about 10 % of otherwise normal persons possess toxoplasma neutralizing anti-bodies. HEIDELMAN found in 6 of 58 normal persons, and CALLAHAN in 2 of 100 normal persons toxoplasma neutralizing anti-bodies in the serum.

Recently the occurrence of asymptomatic toxoplasmosis has been confirmed parasitologically by the discovery of toxoplasma-carriers among human beings (TOMLINSON (1945); KEAN and GROCOTT (1) (1945); SYVERTON and SLAVIN (1946); PLAUT (1946)). Concerning the actual frequency of carrier-toxoplasmosis, we are still in the dark.

We know little or nothing about the factors capable of activating a latent toxoplasmic infection. It is feasible to assume that a decrease in the tolerance of the host plays a part herein.

PINKERTON and WEINMAN witnessed toxoplasmosis made active by an acute Bartonella infection. KLING c.s. surmised that protozoa (toxoplasma?) in the brain were made active by vaccination.

The question arises as to what the effect of pregnancy is on a latent toxoplasmic infection. Mothers of toxoplasmic children have seldom revealed symptoms during pregnancy. Yet JOHNSON c.s. witnessed a recurrent toxoplasmic choroiditis in three successive pregnancies.

Toxoplasmic infection may manifest itself at any age both at a very youthful age, even in the prenatal period, and at a more advanced age. It is not always possible to make a distinction between congenital

and acquired toxoplasmosis (SABIN (3, 5)), since a latent congenital infection actuated post-natally may easily be taken for an acquired infection. It is possible that the presence of anti-bodies in the blood of the mother is an indication of the prenatal origin of toxoplasmosis.

Toxoplasmosis is a hematogenic affection. Dependent on the number and the virulence of the toxoplasmas on the one hand and the susceptibility of the tissue on the other, the reactions vary from mild inflammatory lesions (peri-vascular infiltration, granulomatous lesion) to extensive necrosis. Toxoplasmas, whether accompanied by inflammatory lesions or necrosis or not, have been encountered in the central nervous system, the eyes, the lungs, the heart, the skeletal muscles, the adrenal glands, the pancreas, the pituitary, the liver, the spleen, the lymphnodes, the bone marrow, the kidneys, the ovaries, the testes, the skin and the subcutaneous tissue.

The affinity of toxoplasma for many different organs and tissues produces a clinical picture that is rather variable. It would seem, however, that nervous tissue and in particular young nervous tissue has a special susceptibility to toxoplasma. Toxoplasmosis has in by far the greater number of cases been observed at a very youthful age, manifesting symptoms resulting from predominant neural involvement. The clinical picture of toxoplasmosis at more advanced ages has mostly been determined by predominant extraneural involvement. We would emphatically point out, however, that toxoplasmosis with predominant visceral lesions has been observed in an infant (WOLF, COWEN and PAIGE (5)), predominant neural involvement having been described in an adult by GUIMARÃES.

In PART I of this work we give a review of the literature on Toxoplasmosis. We deal with the epidemiology of toxoplasmosis and the properties of the etiologic agent (Chapter I), then the parasitological, serological and clinical diagnosis of toxoplasmosis (Chapter II), while in Chapter III we give a summary of all reports on the occurrence of toxoplasmosis in man. For the sake of clearness we first mention the cases of toxoplasmosis in infancy, in childhood and in adults, which have been confirmed parasitologically, then we give an outline of the results of serum investigations and mention in conclusion a few cases, in which the diagnosis of toxoplasmosis has been made clinically.

Chapter IV comprises a summary of the clinical and histo-pathological signs in ocular toxoplasmosis. Chapter V is devoted to therapeutic considerations.

In PART II we present 20 cases of proved or presumable toxoplasmic

retinopathy and retino-encephalopathy with associated ocular manifestations. (Chapter VI). We discuss in order of succession the diagnostic procedures and results, the age at onset of symptoms and the mode and source of infection, the cerebral symptoms, the ocular symptoms and the result of family examinations (Chapter VII).

PART I

REVIEW OF THE LITERATURE

CHAPTER I

EPIDEMIOLOGY OF TOXOPLASMOSIS AND PROPERTIES OF THE ETIOLOGIC AGENT

I. EPIDEMIOLOGY

Spontaneous infection by a parasite resembling toxoplasma was first described by LAVERAN in 1900 in paddy-birds (padda oryzivora) in Java [1]).

In 1908 NICOLLE and MANCEAUX witnessed similar micro-organisms in a rodent (gondi) in North Africa and SPLENDORE the same in a rabbit in Brazil. NICOLLE and MANCEAUX gave them the name of toxoplasma because of the crescent-shaped appearance of some micro-organisms [2]).

Since then reports have appeared in many countries on the occurrence of spontaneous toxoplasmosis in a variety of species of animals, including mammals, birds, amphibia, reptiles and fish, in laboratory animals, domestic animals and in wild animals (Table 1). The toxoplasmic nature of the parasites has certainly not been proved in all cases (SABIN (1, 3)).

A wide variety of pathological changes and clinical manifestations have been observed in naturally infected animals. The susceptibility of the different organs and tissues to toxoplasmic infection vary not only from species to species but also in different individuals of the same species. Acute encephalitis is observed in rats, rabbits, mice, guinea-pigs and sheep. In contrast to this type of reaction toxoplasmas in dogs and cats produce lesions in the intestines, lymphnodes, liver and lungs, the central nervous system showing minimal involvement. There may be signs of increasing weakness, loss of appetite, emaciation, dyspnoea, or bloody diarrhoea. Cats may have convulsions in the final stages of a severe infection. It would appear that either the respiratory or the intestinal tract, or both, may be predominantly

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[1]) WENYON (2) is of opinion that the parasites described by LAVERAN are toxoplasmas.

[2]) The Greek "τοξον" means "bow".

TABLE 1

Reports on Spontaneous Toxoplasmosis in Animals

COUNTRY	ANIMAL
United States	Dog (Olafson and Monlux). Cat (Olafson and Monlux). Rat (Perrin c.s.). Sheep (Olafson and Monlux). Guinea pig (Sabin and Olitsky, Markham). Canary (Hegner and Wolfson, Manwell and Herman, Wolfson (1), Herman (1)). Sparrow (Novy and Macneal). Catbird, chipping sparrow, kingbird, red-eyed towhee, song sparrow, swamp sparrow, Baltimore oriole, cowbird, Savannah sparrow (Herman (2)). House finch (Wood and Wood). Pigeon (Johnson).
Argentina	Canary (Rosenbusch).
Brazil	Dog (Migliano, Carini (2), Carini and Maciel (1)). Rabbit (Splendore (1, 2)). Guinea pig (Carini and Migliano). Domestic pigeon (Carini (2)). White throated seedeater, Andean white throat, white bellied swallow, Dominican cardinal, red vamp tanager, yellow finch, palm tanager (Aragao). Rufous-bellied thrush, blue-black grossquit, tyrant flycatcher, white-crested elaenia, king vulture (Carini and Maciel). Tanager (Pessôa and Corrêa).
Mexico	Guinea-pig (Mooser).
French Guiana	Monkey (Thézé).
England	Squirrel (Coles). The Fossa (London Zoological Garden) (Plimmer). Wombat (Welcome Bureau, London) (Coutelen(2)). Vole (Findley and Middleton). Fruit pigeon, pied bush chat (London Zoological Garden) (Plimmer). Snake (London Zoological Garden) (Plimmer).
France	Dog (Boëz, Nicolau and Kopciowska (2)). Rabbit (Levaditi c.s. (3, 5)). Mouse (Nicolau and Balmus (1, 2)). Baboon (Levaditi c.s. (4)). Chimpanzee (Nicolau and Kopciowska(3)) Guinea pig (Nicolau (1), Nicolau and Balmus (2)). Ferret (Coutelen (3)). Waxbills, weaver bird, fire finch, chaffinch (Marullaz). Yellow babbler (Laveran and Marullaz (2)). Lizard (Coutelen (1)).
Danmark	Hare (Christiansen). Dog (Sjolte).
Sweden	Hare (Hülphers c.s.).
Germany	Dog (Yakimoff and Kohl-Yakimoff). Siskin (Walzberg). English sparrow, green finch, linnet (Noller). Domestic fowl (Hepding).
Italy	Dog (U. Mello). Rat (Sangiorgi (2)). Mouse (Sangiorgi (1)). European tree sparrow, Italian house sparrow (Franchini).
Tunisia	Gondi (Nicolle and Manceaux (1, 2, 3), Nicolle and Conor). Dog (Blanc).
Congo	Rabbit (Saceghem).
Senegal	Rabbit (Bourret).
Irak	Dog (Machattie).
Gambia	African vulture (Todd and Wolbach).
India	Dog (Ray and Raghovachari). Domestic pigeon (F. de Mello). Sparrow (Adie).
Dutch East Indies	Rabbit (Brug c.s.). Java sparrow (Laveran).
Japan	Mole (Prowazek). Dog (Hirato). Paddybirds, bamboo finch, Java sparrow (Uegaki (2)).
Formosa	White eye (Uegaki (1)).

affected in natural infection of these animals. The clinical manifestations of toxoplasmic infection in animals such as the dog and the cat may have nothing characteristic about them (SABIN (5)).

There is good reason to assume that clinical inapparent toxoplasmic infection frequently occurs in animals (SABIN (5)).

The occurrence of toxoplasmic infection in a large variety of animals suggests that they are the source of infection in man.

Mode of Natural Transmission: It is certain that the infection in the mother can be transmitted to the child in utero, but how this happens is not exactly known. WOLF, COWEN and PAIGE (1) at first thought it most probable that infection of the placenta leads to infection of the fetus and that the parasites enter the fetal circulation by way of the placenta. Unfortunately there has been only one placenta available for examination and the poor preservation of the placenta in this case made the evaluation of the findings difficult (WOLF, COWEN and PAIGE (5)). WOLF, COWEN and PAIGE (1) also suggested that the amniotic fluid may be affected by an ascending infection from the vagina. The infection might take place either through the intact membranes or through premature ruptures of the membranes, offering a portal of entry for vaginal organisms. The presence of toxoplasma in the cells, lining the alveoli also suggested that aspiration of infected amniotic fluid may be a route of entry of the organism into the fetus (WOLF, COWEN and PAIGE (5)). PINKERTON and WEINMAN suggested that infection might take place during the passage through the birth canal. Vaginal toxoplasmosis has been demonstrated in experimentally infected animals (MESNIL and SARRAILHÉ), but not in man, although ZUELZER reports toxoplasmic lesions of the testes and WOLF, COWEN and PAIGE (5) found lesions without toxoplasmas in the ovaries.

Little is known about the way in which the infection is transmitted from animal to animal and from animal to man.

Some research work done in this field will perhaps give some indications of the possibilities of transmission of the infection. WEINMAN (1) has witnessed congenital transmission in experimentally infected mice. SABIN and OLITSKY allowed starved mice to feed on others dying of the infection and saw that these mice, too, were infected, thus giving evidence that carnivorous animals may acquire the infection by ingestion. OLAFSON and MONLUX made the important discovery that ulcerative lesions with toxoplasmas occur in the intestines of dog and cat spontaneously infected with toxoplasma. They found, too, that the excreta of an infected puppy contained toxoplasma.

SABIN and OLITSKY on the other hand did not succeed in contaminating mice by the excreta of other mice.

In this connection a few observations have been made in man worth mentioning. SABIN (2) mentions that at the time his patient fell ill, the domestic cat had convulsions. The father of the twins with congenital toxoplasmosis described by HEATH and ZUELZER was a municipal employee whose work consisted of collecting refuse. In the performance of his duty he had to handle dead rats as well as to catch live ones.

In the cases mentioned by PINKERTON and HENDERSON of toxoplasmosis in 2 adults there was a history of tick-bites a few days before the onset of the disease. The mother of the child with congenital toxoplasmosis described by BAMATTER (2, 3) was always accompanied by a cat and during the last few weeks of pregnancy had a pruriginous eczema of the legs which was probably caused by flea-bites. The presence of toxoplasmas in the blood of many experimentally infected animals opens up the possibility of the infection being transmitted by biting-insect vectors. Experimental confirmation for this assumption has, however, not yet been obtained. CHATTON and BLANC (2) examined a number of ectoparasites of the gondi, but no toxoplasmas were found here.

PINKERTON and HENDERSON found toxoplasma-laden macrophages in the alveoli and bronchioles and suggested droplet infection as a method of transmission.

Further investigations are necessary to establish either of these methods of transmission for the naturally occurring infections in man and animals. However ingestion of contaminated food, contact with infected excreta, especially of dogs and cats and transmission by insect vectors may play an important role.

II. ETIOLOGIC AGENT

1. MORPHOLOGY AND RELATION TO HOST CELLS

We could not do better than quote someone who has had much experience in the field of human toxoplasmosis and in the field of both experimental and spontaneous toxoplasmosis in animals (SABIN(5)).

"Toxoplasma are highly organized protozoan parasites with distinct cytoplasm and nuclear chromatin. Their size and shape vary with the stage of development and the mode of examination. In the fresh state, as in the examination of a hanging-drop or a cover-slip preparation of an exudate containing toxoplasma or in Giemsa- or Wright-stained air-dried films, they vary in size from 4 to 7 μ in length and

about 2 to 4 μ in width. Multiplication occurs by binary fission and there is no good evidence that schizogony takes place. A recently divided toxoplasma is crescentic in shape with one end pointed and the other slightly rounded. There is no nuclear membrane and the nuclear chromatin often constitutes about a third of the parasite. No flagella or outer membranes are present and there is no evidence of active propelling motion other than the movement of the pointed end in various planes that is seen in fresh preparations. As the toxoplasma grows, it loses its crescentic shape and becomes pyriform, oval or round, prior to division in the longitudinal plane. In Giemsa- and Wright-stained films the cytoplasm takes on various shades of blue and the nuclear chromatin various shades of red to purple.

In sections of fixed tissue, toxoplasma appear only about half as large as in stained films and their appearance is remarkably different, depending on the fixative and stain that is used. After fixation in ZENKER's fluid containing 5 per cent glacial acetic acid and staining with eosin methylene blue, or Giemsa, and sometimes even after staining with hematoxylin and eosin, the toxoplasma are predominantly rounded in shape, the cytoplasm being studded with deep blue or purple granules and containing a clear central zone with a nucleolus-like structure in it, corresponding to the site occupied by the chromatin. On the other hand, after fixation in formalin and staining with hematoxylin and eosin, the more characteristic crescentic or pyriform shape of the toxoplasma is observed and the more familiar appearance of cytoplasm and chromatin as seen in the stained films is found.

All the indications are that toxoplasma are obligate intra-cellular parasites with affinities for practically all types of fixed tissue cells, of both the reticulo-endothelial system and the parenchyma of the various organs. The toxoplasma multiply in the cytoplasm of the host cell until there seems to be nothing left of the cell but a mass of parasites with the nucleus either marginated on the cell wall or extruded. When the toxoplasma are very virulent, the cell membrane ruptures at an early stage and they are then found extra-cellularly in large numbers and in various stages of growth and division. On the other hand, when the toxoplasma are less virulent, or the host cell more resistant, the parasites may continue to multiply and form large aggregates without rupturing the cell membrane, giving rise to forms which have been referred to as cysts or pseudocysts. This would appear to be the entire known cycle of multiplication of the parasite, i.e., invasion of the susceptible cell, intracellular division by repeated binary fission, rupture of the infected host cell with resulting liberation

of the toxoplasma which are then free to invade new susceptible cells. Although it is possible that the time may vary for different strains of toxoplasma and for cells of different grades of susceptibility or resistance, it is known that the cycle within a single cell may take 24 to 48 hours".

The polymorphism and the various stages of development of toxoplasma were closely observed by BRUG and VOS (Fig. 2).

BARNES CROSS prefers to speak of "terminal colonies", consisting of the residual wall of the anucleated host-cell and the enclosed parasites, instead of "pseudo-cysts". BARNES CROSS was in a position to demonstrate a decreased permeability of the surrounding membrane of the host-cell by means of the Feulgen's test. Probably there is no inward penetration of the hosts' anti-bodies nor of therapeutic reagents and no outward escape of the metabolic products of the parasites to induce local inflammatory reactions (BARNES CROSS). "Terminal colony" is a final resistant stage in which the parasites remain inactive for an indefinite length of time.

LEVADITI c.s. (3), LÉPINE and WEINMAN (1) found terminal colonies without tissue-reaction in mice, PINKERTON and WEINMAN in man and PERRIN c.s. in rats. WEINMAN (1) demonstrated by inoculation tests that the terminal colonies continue to be virulent for other animals.

2. CLASSIFICATION

Toxoplasma is classified under the protozoa (NICOLLE and MANCEAUX, SPLENDORE, SABIN, BARNES CROSS). There is a diversity of opinion as to the place of toxoplasma among the protozoa. FRANCA puts it under the hemosporidia, second family: toxoplasmideae. BARNES CROSS, after a profound cytological study, came to the conclusion that it would be premature to classify it definitely further.

The toxoplasmas found in various animals have often been named after the species of animals concerned. Various species of toxoplasmas have been created in this way: toxoplasma gondi (NICOLLE and MANCEAUX), toxoplasma cuniculi (SPLENDORE), toxoplasma avium (LAVERAN), toxoplasma caviae (NIKOLAU), toxoplasma canis (MELLO), toxoplasma talpae (PROWAZEK), etc.

Originally one also employed the term toxoplasma hominis (WOLF, COWEN and PAIGE (3)).

On the ground of their biological and immunological properties we are gradually coming to see that the toxoplasmas of mammals, including man, and perhaps also of birds are identical or at least very

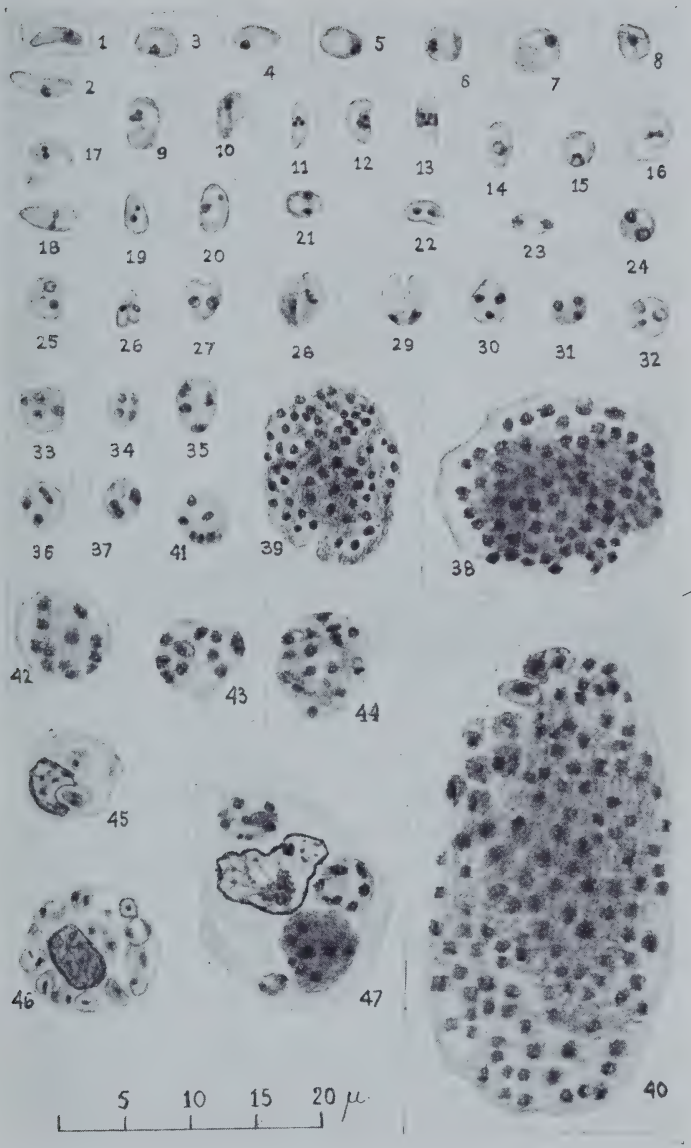

Fig. 2 : Polymorphism of toxoplasma.
(From BRUG and VOS : Ned. Tijdschr. v. Geneesk. 1942)

closely related to each other (SABIN (1, 3), NOBREGA and REIS, JOHNSON). This view was expressed as far back as 1918 by MESNIL.

3. VIABILITY

Toxoplasmas are even more delicate organisms than viruses. They lose their infectivity very rapidly, as well as at high temperature as at low temperature.

Tissues or body fluids which are to be tested for the presence of toxoplasma by animal inoculation should either be inoculated in the fresh state or, when that is not feasible, they may be stored in the refrigerator at about 5° C. for as long as 14 days, provided drying is prevented (SABIN (3)).

4. PROPAGATION

Toxoplasma is an obligate intra-cellular parasite (SABIN and OLITSKY). Attempts, therefore, at cultivating toxoplasmas on artificial media are doomed to failure. Though in vitro propagation has been demonstrated in a medium consisting of surviving susceptible tissue (minced chick embryo), suspended in Tyrode's solution (SABIN and OLITSKY), successful propagation of toxoplasma is only possible by passage in susceptible animals, in which infection can be produced by different routes (intracerebral, intraperitoneal, intravenous, intra-cutaneous, sub-cutaneous, intra-muscular, intra-nasal and oral).

For routine maintenance, one may store infected tissue, such as mouse-brain, submerged in Tyrode's solution in the refrigerator for a period not exceeding two weeks before new animals are inoculated. Some strains of toxoplasma produce a chronic infection in animals, and such animals are an excellent source of toxoplasma since they appear to harbour the parasites almost throughout their lifetime (SABIN (5)).

In experimental toxoplasmosis as in spontaneous toxoplasmosis there is a broad tissue affinity of the toxoplasma. The pathological changes in experimental toxoplasmosis are described by WOLF, COWEN and PAIGE (3) (mice, rabbits, guinea-pig, chicken), SABIN (3) (mice, rabbits), COWEN and WOLF (monkey).

5. DIFFERENTIAL DIAGNOSIS

NICOLLE and MANCEAUX had already distinguished toxoplasma from Leishmania and from trypanosoma on the ground of the absence of a kinetoplast in the toxoplasma.

There is a superficial likeness to sarcocystis. The morphological,

biological and histo-pathological points of difference between toxoplasma and sarcocysts have been outlined by PINKERTON and WEINMAN and by KEAN and GROCOTT (1). Sarcocystis occurs exclusively in striated muscle and connective tissue. PINKERTON and WEINMAN recognized a case described by HERTIG as sarcocystis infection, as toxoplasmosis. KEAN and GROCOTT (1) think that many a case of „sarcosporidiosis" is in reality a case of toxoplasmic-infection.

Toxoplasma exhibits a striking likeness to encephalitozoon. Encephalitozoon has been described first by WRIGHT and CRAIGHEAD, afterwards by LEVADITI c.s. (1) who gave the name, and by many others (see PERRIN (1)). Some authors regard toxoplasma and encephalitozoon as identical (OLAFSON and MONLUX). WOLF, COWEN and PAIGE (1) pointed out a different staining of the two parasites and different tissue-reactions. PINKERTON and WEINMAN mentioned certain morphological differences. PERRIN c.s. made a detailed study of the different staining-methods and the different morphological, histopathological and biological properties in experimental infection (see PERRIN (1, 2)).

Two cases of protozoan infection in man described in the literature on the subject were at first diagnosed as encephalitozoon-infection, but afterwards were recognized as toxoplasmosis (TORRES, WOLF and COWEN (1)). It is not certain if encephalitozoon-infection occurs in man.

CHAPTER II

DIAGNOSIS OF TOXOPLASMIC INFECTION

The etiological diagnosis of toxoplasmosis is made by the morphological and biological identification of toxoplasma (parasitological diagnosis) and by the demonstration of specific anti-bodies in the blood serum (serological diagnosis). Further we must ask ourselves to what extent the clinical manifestations of toxoplasmosis are pathognomonic for this disease (clinical diagnosis). The diagnosis of toxoplasmic-infection is a question of urgency, for, as far as we know, only a very early applied therapy can have any effect.

I. MORPHOLOGICAL AND BIOLOGICAL IDENTIFICATION OF TOXOPLASMA

Organisms of toxoplasmic morphology can be demonstrated in body fluids and in tissues obtained by biopsy (skin, lymphnodes), or at necropsy.

Suspected spinal, ventricular, pleural and peritoneal fluids should be centrifugated and the sediments examined in the fresh state (hanging drop or cover-slip preparation) as well as in stained smears (Kiewit de Jonge, Giemsa or Wright's stain). Toxoplasma has very rarely been seen in blood-films, even from severely infected experimental animals.

In suspected cases with pneumonia it may be of value to examine the sputum.

Tissues should be examined by staining air-dried films (Kiewit de Jonge, Giemsa or Wright's stain) and by preparing sections, preferably not thicker than 4—5 μ. The tissue should be fixed in formaline. Hematoxylin and eosin stains yield most satisfactory results.

Besides the morphological properties the protozoa must also possess the biological properties of the toxoplasma before they can with certainty be identified as toxoplasma (Aragao). The chief characteristic of the toxoplasma is the pathogenicity for a wide range of animals including mammals and birds. Besides they must possess the same immunological properties as toxoplasma (Sabin (1)).

The parasitological diagnosis can, therefore, only be made to per-

fection by the isolation of toxoplasmas by animal inoculation, demonstration of their pathogenicity for a wide range of hosts, and demonstration of the immunological identity with toxoplasmas (cross-immunity experiments).

For animal inoculation centrifugated body-fluids may be employed (cerebro-spinal fluid, blood, urine, peritoneal and pleural exudate, sputum) and emulgated tissue obtained at biopsy or even at necropsy.

In the interpretation of the results of the inoculation tests we must take into consideration the occurrence of spontaneous toxoplasmic-infection in animals. The mouse is highly susceptible to toxoplasma and is presumably least often infected spontaneously. A large number of animals should be inoculated and it should be made certain that no spontaneous toxoplasmosis occurs among the laboratory animals used. SABIN advises a minimum of 6 mice and 3 guinea-pigs inoculated both intra-cerebrally and intra-peritoneally. Sometimes blind passages must be made before the animals reveal any symptoms.

II. DEMONSTRATION OF SPECIFIC ANTI-BODIES [1])

1. SERUM NEUTRALIZING ANTI-BODY TEST

It has already been known for quite a long time that experimentally infected animals are able to recover from acute toxoplasmosis. From re-infection experiments it has been proved that re-convalescent animals possess an immunity the degree, the duration and the mechanism of which has repeatedly been the subject of research-work, but of which as yet we know only too little.

SARRAILHE was the first who examined the serum of dogs and mice recovering or cured of experimental toxoplasmic-infection for neutralizing anti-bodies. For this purpose he injected mixtures of toxoplasma and serum into the peritoneal cavity of mice (mouse protection test). A neutralizing activity of the sera was not observed in these tests.

LEVADITI c.s. (3) examined the mechanism of immunity in experimentally infected rabbits. They inoculated resistant rabbits intra-cerebrally with toxoplasma. Even two hours after the injection they failed to recover the toxoplasma in the brain. Nothing was observed, however, of a toxoplasmacidal activity of a brain-tissue suspension in vitro. LEVADITI c.s. also examined the blood-serum of rabbits for anti-toxoplasmic activity. They did this by injecting rabbits with a mixture of serum and toxoplasma, kept for some hours at 37° C., intracerebrally

[1]) SABIN recently worked out a rapid, microscopical serum test (to be published).

or intra-ocularly. Symptoms did indeed appear, these being caused by toxoplasma. Neither did the blood-serum of immune rabbits injected intra-venously or even intrathecally give protection against intra-cerebral infection of rabbits. LEVADITI c.s. came to the conclusion that the immunity of re-convalescent rabbits could not but be wholly of a cellular nature.

SABIN and OLITSKY have extended their experiments concerning the immunity to various other animals. In the blood-serum of rhesus-monkeys, which had been cured of experimental toxoplasmosis and were refractory to re-infection, they were able to demonstrate "neutralizing" or "protective" anti-bodies by means of the mouse-protection test. In this way the monkey reconvalescent-serum has been found to have a protective effect, whereas the re-convalescent serum of rabbits, dogs and mice has not.

SABIN had already noted that intra-cutaneous injections of toxoplasma in the monkey or rabbit result in skin-lesions, dependent on the quantity and the virulence of the toxoplasma and consisting of local swelling, redness and sometimes necrosis. They availed themselves of this fact by inoculating rabbits with the sera to be tested for neutralizing activity, together with various dilutions of a toxoplasma suspension intra-cutaneously, and by evaluating the neutralizing activity of the serum by the intensity of the skin lesions (rabbit-skin test).

SABIN and RUCHMAN witnessed slight quantities of anti-bodies make their appearance in the monkey-serum as early as 1 week after the infection. After two weeks the titer was at a maximum and remained so for a very long time (the longest period of observation being 14 months). They examined the properties of the toxoplasma neutralizing anti-bodies. The anti-serum was found to neutralize only in vivo. In vitro SABIN and RUCHMAN could find no agglutination, precipitation or lysis of toxoplasma in a mixture of toxoplasma and anti-serum, and after being purged of the serum, the toxoplasmas were found to have retained their virulence.

SABIN and RUCHMAN discovered two properties of the toxoplasma neutralizing anti-body which must certainly be reckoned with nl. the low titer and the thermolability of the anti-body. The strongest anti-sera neutralized at most 100 minimal skin lesion doses completely. No anti-bodies were any longer to be seen even in a serum diluted to $^1/_{10}$. It was found that at a normal temperature and even at + 4° C. the neutralizing activity of the anti-serum, even after a few days diminished and after keeping it a fortnight at + 5° C. was completely gone. On the application of heat over a period of half an hour at 56° C. the

anti-body was wholly destroyed. If the serum could not be examined at once it was found that it was best to preserve it at a low temperature (dry ice box) or even in a dry state (freeze drying).

The presence of toxoplasma neutralizing anti-bodies in the serum of re-convalescent monkeys is not accompanied by a chronic toxoplasmic-infection according to SABIN and RUCHMAN. They found no toxoplasmas in 2 monkeys with anti-bodies in the serum 14 and 17 weeks respectively after infection, not by direct histological examination nor by animal passage. WEINMAN, however, was not satisfied with SABIN and RUCHMAN's experiments. He found virulent toxoplasma in the brain of some mice which had survived an experimental toxoplasmic-infection.

The immunity that develops in animals after experimental toxoplasmosis rests presumably not on the presence of neutralizing anti-bodies, since they are neither found at all (mice, dogs, rabbits) or only in small quantities (monkey). On the whole the immunity in toxoplasmosis exhibits a likeness to the immunity caused by various kinds of viruses, just as the toxoplasma in other respects shows a resemblance to viruses (obligate intra-cellular parasitism, SABIN and OLITSKY).

In 1941 SABIN (2) discovered toxoplasma neutralizing anti-bodies in human serum, nl. in a boy of 6 years, who died of a toxoplasmosis confirmed parasitologically. SABIN found anti-bodies 10 days after the onset of the sickness till shortly before death on the 30th day after the commencement of the illness. Toxoplasma neutralizing anti-bodies have been recorded many times in human serum since then by SABIN and many other authors. It appeared that the anti-bodies in man are to be found years after the illness.

The method of carrying out the toxoplasma neutralizing anti-body test according to SABIN and OLITSKY's technique (rabbit-skin test) is as follows:

"Animals. Clear-skinned, well-nourished rabbits, weighing about 3 kg give the best results. The hair is clipped with an Oster animal clipper (000 or 0000). A naturally immune rabbit is recognized by the fact that small, rapidly regressing or insignificant skin lesions develop with the control mixtures and the animal survives at a time when other rabbits inoculated simultaneously with the same toxoplasma suspension develop the usual progressive lesions and die.

Serum. Whenever possible the serum is used on the day of bleeding. Sera which has been in the refrigerator overnight or in the mail for 24 to 48 hours (during the winter months) have also yielded positive results. The unused portion of each serum is frozen rapidly in a lusteroid container and stored in an insulated box containing solid CO_2 to permit repetition of the test whenever necessary. Serum which cannot be tested within 24 hours of bleeding is similarly frozen and stored in the CO_2 refrigerator.

Toxoplasma Suspension. The brains of mice succumbing 4 days after intracerebral inoculation are examined by means of Wright-stained films to make certain of the presence of large numbers of toxoplasma and the absence of bacteria. At least 2 such brains are ground in a mortar without an abrasive and enough Tyrode's solution is added to make a 10 % suspension. This suspension is then allowed to sediment spontaneously for 30 minutes in an ordinary refrigerator. From the opalescent supernatant liquid which is regarded as the 1 : 10 dilution, the 1 : 50, 1 : 500 and 1 : 5000 dilutions are prepared using Tyrode's solution as the diluent. Mixtures consisting of 0,15 cc of undiluted serum or Tyrode's solution (for the control) and 0,15 cc of each of the above dilutions thus yield final dilutions of toxoplasma-containing mouse brain suspension of 1 : 20, 1 : 100, 1 : 1000 and 1 : 10.000. After thorough shaking these mixtures are left at room temperature for 30 minutes before inoculation. The back of each rabbit is marked off into 20 squares with an indelible pencil to accommodate all the dilutions of the Tyrode's solution control and 4 sera. 0,2 cc of each mixture is injected intracutaneously.

Interpretation of Results. All human sera produce erythema and oedema in the rabbit's skin within 24 hours, but this reaction has usually disappeared by the 4th day when the toxoplasma lesions begin to appear. The toxoplasma skin lesions are raised, indurated and the ones resulting from the larger concentrations undergo central necrosis ; they are fully developed by the 7th or 8th day, when a record is made by tracing on transparent paper the size of each lesion and of the area of necrosis. The skin lesions begin to blanch after the 8th day and the rabbits with very rare exceptions die of a generalized toxoplasmosis between the 9th and 12th day. The mixtures with most of the distinctly negative human sera yield skin lesions which are somewhat larger than the Tyrode's solution controls (SABIN (4))".

Other authors have introduced slight modifications. WOLF, COWEN and PAIGE (6) injected 6 toxoplasma-dilutions between 1 : 20 and 1 : 1600. With these dilutions differences with the control-injections would come out more clearly. They make 3 control-tests, nl. 2 with normal sera and 1 with isotonic saline solution. HEIDELMAN omits the 1 : 10.000 dilution. CALLAHAN injects 5 toxoplasma dilutions, nl. 1 : 20, 1 : 100, 1 : 200, 1 : 1000 and 1 : 5000.

SABIN classifies the sera as negative, equivocal, positive and strongly positive (Table 2). WOLF, COWEN and PAIGE (6) call the test positive : "when the test serum lesions and the central areas of necrosis are in general one-half or less the size of the control lesions and are entirely inhibited in the higher dilutions of the suspension of toxoplasmas at which control lesions still appear" ; suggestively positive : "when the differences are distinct but less pronounced" ; doubtful : "when the contrast is minor" ; and negative : "when the contrast is absent". JOHNSON c.s., too, judge the skin lesions according to the extension. They speak of "positive" when the serum-lesion is half or less than half of the corresponding control-lesion. CROTHERS calls the result of the test "strongly positive", "positive", "moderately positive", "doubtful" and "suggestive", without giving any further details about the criteria.

TABLE 2

Criteria Used in Interpretation of Toxoplasma Neutralization Tests
(SABIN (4))

Category of unknown serum	Relative size of skin lesions yielded by mixtures containing various dilutions of infected mouse brain suspension			
	1 : 20	1 : 100	1 : 1000	1 : 10.000
Negative	++++	++++	+++	++ or +
Negative	++++	++++	+++	0
Equivocal (Repeat test)	++++	+++	++ or +	0
Positive	++++ or +++	+++ or ++	0	0
Strong positive.....	++	0	0	0

Categoric criteria for what constitutes a positive result are not formulated.

SABIN and OLITSKY were the first to point out the diagnostic value of the neutralization test in toxoplasmosis. "It is", says SABIN „important to remember that a positive neutralization test may be indicative only of past toxoplasma-infection, unless it can be shown to appear during the course of the illness". "A negative result would not permit one to rule out the possibility of toxoplasmic-infection".

2. COMPLEMENT FIXATION TEST

Some authors have mentioned the presence of specific, complement fixing anti-bodies in the blood of various species of animals, and also in man.

NICOLAU and RAVELO used a methyl-alcohol extract of the dried spleen of rabbits infected with toxoplasma as an antigen. They reported a positive result with the serum of experimentally infected rabbits.

SABIN and WARREN (1) prepared an antigen by a 10 % suspension of infected rabbit-brain to be kept at 4° C. for 18 hours, after this to be frozen and thawed 5 times alternately and to centrifugate this suspension for 30 minutes. The super-natant fluid was used as an antigen. A control-antigen was made in the same way from normal rabbit-brain. They obtained positive results with it. If they used organs rich in toxoplasmas for the preparation of the antigen, they got a negative result (mouse-brain) or a non-specific fixation (mouse-lung). In contradistinction to NICOLAU and RAVELO, SABIN and WARREN found no complement fixing anti-bodies in the serum of experimentally infected rabbits, neither in the serum of experimentally infected

dogs and cats, but they did in the serum of infected rhesus-monkeys and in man. They found anti-bodies in the monkey-serum as early as 1 week to 4 weeks after the infection, but after two months the titer appeared to be very low or gone altogether.

SABIN and WARREN found complement fixing anti-bodies in 10 human sera. Toxoplasma neutralizing anti-bodies were found in 8 of these sera ; the serum of one patient and of his mother contained complement-fixing anti-bodies only.

The method of carrying out the complement fixation test in toxoplasmosis is the same as that employed in other complement fixation tests. The difficulty lies in the preparation of a suitable antigen. It is desirable to examine the sera within 24 hours after the removal of the blood, as SABIN and WARREN observed that normal monkey-serum, after being kept in a refrigerator spontaneously acquired a complement fixing activity. In the serum of 20 patients with already inactive infection, SABIN and WARREN did find toxoplasma neutralizing anti-bodies, but no complement fixing anti-bodies. The complement fixation test is, therefore, of importance to a rapid diagnosis of acute toxoplasmosis only.

III. CLINICAL DIAGNOSIS

The chances of a clinical diagnosis of toxoplasmosis do certainly not exist in all cases, as toxoplasmosis is a generalized affection, and may manifest symptoms of a very divergent nature. However, the syndrome which occurs in many cases of toxoplasmosis at a very early age and which is caused by a disseminated affection of the central nervous-system, is worth mentioning.

The clinical picture of infantile toxoplasmic encephalomyelitis in the active stage shows the following characteristics (WOLF, COWEN and PAIGE (6)) : 1. onset at birth or shortly thereafter ; 2. convulsions ; 3. hydrocephalus, clinically apparent or demonstrable by pneumencephalography ; 4. other inconstant neurologic symptoms, such as tremors, twitches, spastic contraction of the extremities and evidence of transverse myelitis ; 5. bilateral, focal chorioretinitis, almost invariably involving the macula ; 6. other ocular signs, such as microphthalmos and ocular palsies ; 7. intra-cerebral calcification, often multiple and bilateral and involving the cerebral cortex and basal ganglia ; 8. neonatal jaundice, occasionally lasting many weeks ; 9. hepatosplenomegaly, which occasionally may last for many months ; 10. insterstitial pneumonitis ; 11. xanthochromia, moderate round

cell pleocytosis and high protein content of the cerebro-spinal fluid; 12. occasional anemia and leucopenia.

If the acute stage is survived, the syndrome is characterized by the following residual effects of the infection (WOLF, COWEN and PAIGE (6)): 1. healed or inactive chorioretinitis; 2. reduced vision; 3. strabismus, nystagmus and microphthalmos; 4. persisting intracerebral calcification; 5. continuance or late appearance of generalized convulsive seizures or petit mal attacks; 6. chronic hydrocephalus; 7. retardation of speech development, and 8. mental deficiency, usually mild.

The outstanding clinical findings in infantile toxoplasmic encephalomyelitis, constitute a tetrade of clinical signs (SABIN (5)):

1. Internal hydrocephalus or microcephalus.
2. Convulsions or other nervous disturbances (spasticity, reflex-abnormalities, mental deficiency).
3. Chorioretinitis and other ocular signs.
4. Röntgenographic evidence of cerebral calcifications.

Toxoplasmic encephalomyelitis is characterized by disseminated, chronic, necrotizing and granulomatous lesions. Internal hydrocephalus may be caused by an obstruction of the ventricular system or by an extensive destruction of the brain-tissue. The head may be of normal size, hydrocephalic or microcephalic. The neurological symptoms vary. In the active stage the cerebro-spinal fluid is frequently xanthochromic containing few if any cells, but often a very high protein content (albumino-cytologic dissociation). The colloidal tests show the parenchymal type and the tryptophan-test may be strongly positive (FREUDENBERG).

The question is often asked if calcification of the lesions is typical of toxoplasmic encephalitis. The question must be answered in the negative. The precipitation of calcium-salts in the central nervous-system may occur in any chronic degenerative process accompanied by low tissue-metabolism (SPIELMEYER). Except in non-inflammatory conditions such as traumatic lesions, tumors and tumor-like formations, disturbances in the calcium-metabolism, calcification of the brain-vessels, intracerebral calcification may occur in all forms of fetal or infantile necrotizing encephalopathy (tuberculosis, syphilis, toxoplasmosis). For a full discussion of the röntgenographical findings in infantile toxoplasmosis, we refer the reader to DYKE c.s. In Part II we shall try to give an outline of the clinical picture of ocular toxoplasmosis.

The combination of chorioretinitis and encephalitis is hardly anywhere to be found in ophthalmological literature. MENSCHALLIK found

choroiditis in 3 % of the congenital imbeciles, while UHTHOFF met an old chorioretinitis in 2 % of the imbeciles. According to BEST this would seem to show that congenital syphilis was the cause of both chorioretinitis and imbecility (UHTHOFF : Handbuch der gesamte Ophthalmologie, Graefe-Sämisch, Bd. II, 303, 1451, 1489, 1544). An examination conducted by ourselves of 100 post-encephalitic or chronic-encephalitic imbeciles also showed 2 patients with chorioretinitis (Part II: Own Observations: case 16 and 17). Congenital syphilis was out of the question.

That the syndrome of chorioretinitis and encephalitis are not so infrequent is moreover borne out by the frequency in which intracerebral calcifications are encountered in congenital or infantile chorioretinitis. Various authors deem the presence of inactive chorioretinitis and intracerebral calcification of great significance to the retrograde diagnosis of infantile toxoplasmosis.

PINKERTON and HENDERSON described fever, spotted-fever-like exanthema and atypical pneumonia in two adults with toxoplasmosis. It is certain that these are not the only manifestations of adult toxoplasmosis.

CHAPTER III

REPORTS ON HUMAN TOXOPLASMOSIS

In several cases "toxoplasma-like structures" or „toxoplasmas" have been described in man of which it is doubted whether it is really toxoplasma-infection.

We mention here a statement made by CASTELLANI (1914), who described "parasites" in the blood and in the spleen of a 14-year-old boy, who died in Ceylon of a disease characterized by fever, anemia and splenomegalia. CASTELLANI was of opinion that he was concerned with toxoplasmas and called the parasites „toxoplasma pyrogenes".

This also applies to an observation made by FEDOROVITCH (1916), who on the Black Sea likewise found suchlike "parasites" in the blood of a boy with the same clinical picture and also of a statement made by CHALMERS and KAMAR (1920) about a "parasite" in the spleen of a man with chronic fever and intestinal trouble, in the Sudan. WENYON (1) very much doubts the morphological similarity of the forms in these cases to toxoplasmas and rather regards them as yeast cells or cell-remnants.

In 1931 BLAND wrote that he had isolated "toxoplasmas" in a rabbit that had been inoculated with the blood of a patient suffering from "glandular fever" (infectious mono-nucleosis). SABIN (1) points out that the circumstances under which this took place do not justify the conclusion that the protozoa originated in the blood of the patient.

SABIN (2) mentions en passant that BAUER and COGGESHALL, who occupied themselves with yellow fever showed him necrotic lesions in the liver, in which "toxoplasma-like structures" were present.

Some time ago DRENOWSKI mentioned that during routine examinations of blood-films at the Malaria-Institute, Börgas in Bulgaria he hit upon toxoplasmas in the blood by chance. He was not in a position to communicate any further details about the patient.

There are also several other statements on the possible protozoan nature of affections known under another term.

In one of his articles on experimental toxoplasmosis LEVADITI surmised that certain bodies appearing in one of SPIELMEYER's illustrations on familiar amaurotic idiocy might be parasites of the toxoplasma-group and attempts in this way to associate familiar amaurotic idiocy with protozoan encephalitides.

KLING c.s. found protozoan parasites in the brain in 5 cases of postvaccinal encephalitis and stated that there was some connection between the quantity of parasites and the severity of the lesions. They think that the protozoa were activated by the vaccination. There is a resemblance between the protozoa and the toxoplasmas.

NEGRI entertained the possibility of the characteristic "Negri-bodies" in rabies-encephalitis being parasites. MANOUELIAN and VIALA spoke recently of the parasitic nature of the Negri-bodies and termed them „encephalitozoon rabiei". LEVADITI, too, observed the likeness to encephalitozoon cuniculi, but classified them separately under the term of "Glugea lyssae". Most authors, however, consider the Negri-bodies to be cytoplasmic inclusions.

The "minute bodies" described by HASSIN in 1927, were considered by him to be toxoplasmas in 1940. He found these "minute bodies" in the brain of a child that died 2 weeks after birth of an acute meningoencephalitis. Besides this, the child had multiple congenital malformations. HASSIN at first surmised that he was concerned with acute epidemic encephalitis, because the histopathological changes in the brain resembled those in experimental epidemic encephalitis.

Except for the histopathological description of the brain HASSIN gave few particulars about the child which was a twin. WOLF, COWEN and PAIGE (5) deem the clinical data too inadequate and the histopathological description too divergent-to say nothing of the doubtful nature of the so-called „minute bodies"-to simply assume this case to be toxoplasma-infection.

In a number of cases, however, the diagnosis of toxoplasmosis was of a more convincing nature. The diagnosis here is based either on biological and morphological identification of the parasites as toxoplasmas, or on exhibiting specific serum-properties. In a number of cases the presumed diagnosis was made on the ground of the characteristic symptoms of infantile toxoplasmosis.

I. BIOLOGICAL AND MORPHOLOGICAL IDENTIFICATION OF TOXOPLASMA

A. IN INFANCY

1. TRANSMISSION OF THE INFECTION TO ANIMALS

Almost forty years after the discovery of toxoplasma as a new protozoan parasite, it was known with certainty that the same protozoon was an agent causing disease in man.

In June 1938 the Americans WOLF, COWEN and PAIGE isolated a protozoan parasite from the brain of a child, who died 31 days after birth with cerebral symptoms. They had had this child under observation in New-York (WOLF, COWEN and PAIGE (1)).

Case C. D. (WOLF, COWEN and PAIGE) is a male infant who had convulsions even on the third day after birth. In the further course there were respiration-troubles and symptoms of an affection of the spinal cord. There was enophthalmus present on the left side. Nystagmus and deviation of the eyes are also present. In the fundus oculi there were originally no abnormalities observed, but repeated examination a few days prior to death revealed an irregular reddish-brown area in each macular area about 1 disc diameter in size. These changes were interpreted as resulting from hemorrhage associated with multiple injuries of the central nervous-system sustained in the course of delivery.

On a post-mortem examination being held, however, the clinical diagnosis proved to be incorrect and the histo-pathological substratum of the symptoms to be a "widespread granulomatous encephalo-myelitis characterized by focal areas of inflammation, necrosis with tendency to become calcified and disseminated miliary granulomas". The ophthalmoscopic picture observed appeared to have been caused by a localized chorioretinitis.

WOLF, COWEN and PAIGE described the presence of a large number of protozoa in many lesions in the brain, in the spinal cord and also in the eyes. Moreover they succeeded in showing that these protozoa were pathogenic to various species of animals by inoculating the animals with an emulsion of brain tissue of the child, which they prepared during the autopsy. They issued a provisional report on these animal experiments in 1939 (WOLF, COWEN and PAIGE (2)), followed by a full report of their findings in 1940 (WOLF, COWEN and PAIGE (3)).

After they had succeeded in transmitting the infection to laboratory animals, their supposition based on morphological grounds was confirmed that the protozoa, which they held responsible for the inflammatory changes in the central nervous-system and in the eyes, were toxoplasmas. The micro-organisms in the experimental inflammatory lesions corresponded in every way to those toxoplasmas of animal origin, which SABIN and OLITSKY had isolated from a guinea-pig in 1935 (Rockefeller Institute animal strain of toxoplasma). The

course of the disease and the nature of the lesions were likewise identical to the course and the lesions appearing in the experimental infection with the toxoplasma of animal origin. The wide host-range of infectivity characteristic of the toxoplasmas was also found to exist, since rabbits, mice, guinea-pigs as well as chickens were found to be susceptible to the infection with the human protozoa. Most convincing, however, were the cross-immunity experiments. The provisional term given by WOLF, COWEN and PAIGE to their isolated toxoplasma is "toxoplasma hominis". SABIN (1) confirmed later on the identity of "toxoplasma hominis" once more with the toxoplasma-strain isolated by him in 1935 from a guinea-pig.

WOLF, COWEN and PAIGE were now the first to speak of "toxoplasmic encephalomyelitis".

Shortly after this WOLF, COWEN and PAIGE (5) again described a case of encephalomyelitis in a new-born child that terminated fatally.

Case L. M. (WOLF, COWEN and PAIGE): Even 2 hours after delivery of a prematurely born child it was observed that hydrocephalus was present. In the further course the hydro-cephalus increased. On a röntgenographic examination being held on the 6th day, cerebral calcification was encountered. Even during the first few weeks the existance of a bilateral microphthalmy and membranous masses in the vitreous were noted. Later on convulsions and tremors developed. The cerebro-spinal fluid was xantho-chromic and contained much protein. The child died at the age of 9 weeks.

There appeared to be a diffuse necrotizing encephalomyelitis with miliary granulomata and extensive calcification. The foramina interventricularia and the aquaeductus Sylvii were shut off and the ventricles considerably dilated.

There was chorioretinitis present in both eyes.

WOLF, COWEN and PAIGE again encountered toxoplasmas in the lesions in the brain, spinal cord and also in the eye. Moreover they also succeeded this time in transmitting the infection to mice and in identifying the infection as toxoplasmosis on the ground of the morphology of the micro-organisms, the course of the experimental disease, the nature of the histo-pathological changes, the pathogenicity and the cross-immunity phenomena (L.M. strain of human toxoplasma). In this way they have proved the existance of infantile toxoplasmic encephalomyelitis a second time.

WOLF, COWEN and PAIGE (6) likewise observed toxoplasmosis in 1 of 3 mice, which had been inoculated with the cerebrospinal fluid of a $7\frac{1}{2}$-week-old child. The toxoplasmosis could be transmitted serially. WOLF, COWEN and PAIGE summarized the case as follows:

Case J. F. (WOLF, COWEN and PAIGE): A boy, born at full term, was jaundiced at birth, and shortly afterwards enlargement of the liver and spleen developed. Separation of the cranial sutures and bulging of the anterior fontanel were observed at 26 days of

age. Röntgenographic examination of the skull confirmed the presence of internal hydro-cephalus and, in addition, demonstrated a number of areas of calcification in the cerebrum. At the age of 31 days ophthalmoscopic examination disclosed multiple foci of chorioretinitis in both eye-grounds. There was slight left microphthalmos. The cerebro-spinal fluid proved to be xanthochromic and showed an increase in total protein and cells. Jaundice disappeared at 7 weeks of age. The spleen was no longer felt at 7½ months of age, while the liver was still palpable. The head remained hydrocephalic, and the child appeared to be seriously retarded in psychomotor development.

An examination of the serum of the child at the age of 8 months for toxoplasma neutralizing anti-bodies was positive.

GUIMARÃES witnessed a child of 14 months in Brazil with probable toxoplasmosis.

The GUIMARÃES case: The child is suffering from congenital hydrocephalus, fever, diarrhoea, convulsions, tremor of the right arm and nystagmus. The X-ray photograph of the skull showed intra-cerebral foci of calcification and a röntgenographic examination of the extremities revealed the absence of ossification at the end of the long bones. The cerebro-spinal fluid was xanthochromic and the percentage of protein and the number of cells had increased.

GUIMARÃES isolated toxoplasmas in guinea-pigs and mice, which had been inoculated with the cerebro-spinal fluid of the child.

In the autumn of 1945 we, ourselves, saw a patient in the south of Holland 6 years old suffering from a chronic encephalitis and recurrent chorioretinitis with all the clinical characteristics of infantile toxoplasmosis (BINKHORST (1, 2, 3)). On attempts being made to transmit the infection by means of inoculation with cerebro-spinal fluid to laboratory animals, parasites resembling toxoplasmas were observed. Later on we obtained further confirmation of the diagnosis of congenital toxoplasmosis by the presence of toxoplasma neutralizing anti-bodies in the blood of the child and of the mother (see Part II: Own Observations: Case 3).

KEAN and GROCOTT (2) make mention of congenital toxoplasmosis in Panama.

Case of KEAN and GROCOTT: A premature child became cyanotic soon after birth respiration becoming irregular. There were no convulsions. The child died 10 hours after birth. On an autopsy being held, KEAN and GROCOTT found a necrotizing, calcifying, principally focal encephalomyelitis. The structure of the brain had for the greater part broken down. The cerebral-membranes were hemorrhagic and infiltrated. In the eye an intense granulomatous chorioretinitis was present and also an inflammatory reaction in the optic nerve. Further signs of inflammation were found in the nervus trigeminus, nervus femoralis, lungs, heart, bladder, tongue and striated muscles. Parasites, single and in cystlike aggregates, were encountered in the central nervous system, the eye, nervus trigeminus, kidneys, bladder, tongue, striated muscles and nervus femoralis. Although 31 hours had elapsed since death, they succeeded in causing

an experimental toxoplasmosis in guinea-pigs by means of inoculation with an emulsion of cerebral-tissue.

Hence this case could not only be identified as toxoplasmosis by autopsy but also experimentally on animals. Although in this case it was clearly proved that toxoplasmosis is a systemic disease, there was a special affinity of the parasite to nervous tissue. It was for the first time that parasites have been described in the peripheral nerves of man.

Finally DAVEL, VAN DER ELST, WINSSER, VAN THIEL and VERLINDE (1948) made a very interesting observation of toxoplasma-infection in an infant. During routine examination of the cerebrospinal fluid the presence of toxoplasmas in the sediment had already been observed. The infection was transmitted to mice by means of intracerebral inoculation with ventricular fluid and a toxoplasma-strain was isolated in this way (Bk.-strain). The child died when 13 weeks old. The autopsy confirmed the diagnosis of toxoplasma-encephalitis.

For further details of this case including the eye-symptoms, we refer the reader to Part II : Own Observations : case 2.

2. MORPHOLOGICAL IDENTIFICATION OF "TOXOPLASMA-LIKE STRUCTURES"

Whereas more or less convincing evidence of the toxoplasmic etiology of certain infantile forms of encephalomyelitis has been brought forward in a few cases by the transmission of the infection to laboratory-animals, several other cases have been described, in which on being examined microscopically, micro-organisms resembling toxoplasma were encountered.

The identity of the clinical symptoms, the occurrence in newborn children, the exclusion of other possible infections and the resemblance of the histo-pathological findings to those in "toxoplasmic encephalomyelitis", are the grounds on which these cases are generally accepted as instances of toxoplasmic encephalomyelitis, although, as SABIN (2) has rightly remarked, "evidence in these cases is only probable."

The very first observation of such a case was published in Cecho-Slovakia as far back as 1923 by the Prague ophthalmologist JANKÛ. Unfortunately JANKÛ published his case in Cech exclusively, which accounts for the fact that it has not drawn the attention it deserves [1]). The most detailed report on JANKÛ's article is given by WOLF and COWEN (1) in English.

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[1]) JANKÛ intends to have this publication translated into a more current language (personal communication).

JANKÛ gave a description of the eyes of a child with enormous hydro-cephalus.

The JANKÛ case : A child of eleven months, born of normal pregnancy and labor had a left microphthalmus since birth, blindness from the age of three months and a gradually increasing hydrocephalus. In the fundi of both eyes, JANKÛ noted a so-called macular coloboma.

When the child died at the age of 11 months, there was unfortunately no opportunity of examining the brain microscopically. If this had been done, an encephalo-myelitis would presumably have been found with changes identical to the now well-known inflammatory symptoms of toxoplasmic encephalomyelitis.

JANKÛ, however, has been in a position to examine both bulbi oculi microscopically and has succeeded in ascertaining that, in the main, inflammatory changes of a chronic nature in the retina and choroid membrane formed the substratum of the so-called macular coloboma. Moreover, JANKÛ described in the retina of one of the eyes "parasitic cysts" which he termed sporocysts and which were filled with smaller organisms, sporozoites. JANKÛ classified the parasites under the group of sporozoa of the Protozoa, although he emphatically states that the classification of the protozoa was no easy matter for him. His classification of the micro-organisms under the sporozoa was consequently a subject of criticism. LEVADITI, who had much experience in the field of experimental encephalomyelitis due to encephalitozoon cuniculi and toxoplasma cuniculi (LEVADITI c.s. (1)), was struck by the resemblence of the protozoa in JANKÛ's slides to encephalitozoon and to toxoplasma. He says : "l'Examen des préparations de JANKÛ m'a fait l'impression qu'il s'agissait de Protozoaires dont la ressemblance avec certains stades évolutifs de l'Encephalitozoon cuniculi (pansporoblastes) était frappante". On the other hand he points out the likeness that the hydrocephalus bears to internal hydrocephalus which he observed in the infection of rabbits with toxoplasma cuniculi as a consequence of an inflammation of the plexus choroideus. LEVADITI was, therefore as far back as 1928, strongly inclined to believe that JANKÛ had described a case of human toxoplasmosis, which supposition was shared later on by other authors. Since the toxoplasmic character of JANKÛ's parasites has in the meanwhile become so probable and the clinical and histo-pathological picture shown by the patient bears such a great likeness to the cases described afterwards as toxoplasmic chorioretinitis, we assume, so long as it is not yet determined, that other protozoa resembling toxoplasma may cause the same ocular-disease, that JANKÛ has described the first case of ocular toxoplasmosis.

Another case, which is now generally regarded as a case of toxoplasmosis, is a case observed by C. MARGARINOS TORRES in Brazil in 1927.

TORRES's case concerns a full-term infant dying at the age of 2 days and presenting generalized muscular contractions and convulsions shortly before death.

An autopsy was held and "foci of meningo-encephalo-myelitis" were found in the brain, which were "quite similar to those which one meets in Chagas' disease and in experimental toxoplasmosis". Further "disseminated foci of myositis" and „acute diffuse myocarditis" were found. Unfortunately, TORRES mentions hardly any clinical symptoms and no other histological findings than those indicated above. He mentions the presence of intra-cellular "presumably protozoan" parasites in the inflammatory lesions.

TORRES found that these protozoa resemble encephalitozoon cuniculi most, and that the inflammatory lesions bear a likeness to those in "Chagas' disease". He therefore termed the parasites "encephalitozoon Chagasi" and assumed an intra-uterine infection as the cause of the disease.

LEVADITI entertained the possibility of these parasites being toxoplasmas.

WOLF and COWEN (1) supplied a detailed contribution to the knowledge of protozoan infections of the central nervous-system by their article in 1937 in reference to a case of encephalomyelitis, observed in New-York, that presumably was also of a fetal nature.

Case J. S. (WOLF and COWEN): From her birth onward this girl manifested convulsions, retraction of the head and twitching movements of the extremities. The head was slightly enlarged; the anterior fontanel was enlarged and bulged. There was hyperactivity of the deep reflexes and the Babinski sign was present on both sides. The pupils reacted sluggishly to light. There was a high protein content and pleocytosis in the cerebrospinal fluid, that was xanthochromic. An ophthalmological examination was made on the 28th day, shortly before the death of the child, little of which, however, has been recorded. WOLF and COWEN found in both fundi slightly elevated, yellowish-white lesions, which they recognized as inflammatory lesions.

When the child died on the 30th day after birth, there was actually a disseminated necrotizing granulomatous encephalomyelitis and also a focal chorioretinitis. WOLF and COWEN found in the inflammatory lesions parasites resembling encephalitozoon cuniculi, which they termed originally "encephalitozoon hominis". SABIN, however, who has had much experience in toxoplasmas, thinks he recognizes toxoplasmas in these parasites. When, therefore, some years afterwards, WOLF, COWEN and PAIGE (2, 3) demonstrated beyond any doubt that

toxoplasma-infection is capable of causing a clinical and histo-pathological picture, that the case described by them in 1937 was quite identical, they, too, no longer doubted at all that they had been concerned with a case of "toxoplasmic encephalomyelitis".

In the meantime WOLF and COWEN (2) have recognized in descriptions of infantile necrotizing encephalomyelitis found in the literature a case, the protozoan nature of which they were in a position to determine, and which they consider identical to the observation made by themselves.

In 1936, RICHTER gave a histo-pathological description of a case of "meningo-encephalomyelitis neonatorum".

RICHTER's case: A girl of 7 weeks has exhibited symptoms for a week. She has convulsive twitchings and clonic spasms of the arms and legs, opisthotonos and fever. The spinal fluid was xanthochromic, contained red blood cells and 30 white blood cells per cmm., and a protein content of 1260 mgr./100 cc. There were no findings suggestive of congenital syphilis. At autopsy changes for the greater part in the nervous system were found to be present. The eyes were not examined. There were widespread focal, chronic inflammatory lesions in the central nervous system, frequently associated with necrosis, the ventricular walls being severely involved and disseminated miliary granulomas being present. There was a focal leptomeningeal reaction. Scattered calcium deposits were found. The apparent age of some of the lesions and the absence of developmental defects made it probable that the process had its inception late in gestation.

In view of the histo-pathological changes, RICHTER considered the possibility of a congenital syphilitic meningo-encephalitis, but abandoned this diagnosis because no syphilitic changes were encountered in other organs. Hence the cause of the disease remained obscure till WOLF and COWEN re-studied the microscopical slides and discovered parasites, individual and in clusters, in the inflammatory lesions, identical to the parasites they had found in their own case. The discovery of these parasites together with the identity of the clinical picture and the pathological process render it probable that both cases are of the same etiology.

PINKERTON and WEINMAN re-examined a case described by HERTIG in 1934.

HERTIG's case: A 2-month-old, prematurely born child has been suffering from diarrhoea and omphalitis since birth. The child dies 25 days old with symptoms of terminal broncho-pneumonia and dilatation of the heart. On an autopsy being held HERTIG found abscesses in the cerebral-hemispheres, foci of purulent meningitis and peritonitis. From the peritoneal exudate and from the cerebral abscesses he cultivated bacillus coli, staphylococcus albus and staphylococcus aureus. As a chance discovery HERTIG describes protozoa in the myocard, which he regards as atypical sarcocystis

PINKERTON and WEINMAN also found these protozoa in the brain and lungs and the adrenals and took them for toxoplasmas. Around the parasites there were few if any inflammatory or necrotic changes. Evidently death was caused in this case by a concomitant bacterial infection.

The first communication concerning the occurrence of toxoplasmosis in Holland came in 1941. The case had been observed by C. DE LANGE more than 12 years prior to this time, but had not been recognized as such.

She made a full report of this case in 1929 under the diagnosis of "hydro-cephalus chronicus acquisitus", due to meningo-encephalitis e causa ignota (C. DE LANGE (1)). That the true cause was toxoplasma-infection and DE LANGE, without being aware of this, gave a clinical and histo-pathological description of a case of infantile toxoplasmic encephalitis, was not to come to light until 12 years later. WOLF, COWEN and PAIGE discovered at the time in the description of the case, a clinical and histo-pathological resemblence to the cases which had been identified by them in the meantime as cases of infantile toxoplasmic encephalomyelitis and urged for a more detailed analysis of the slides, which had fortunately been preserved.

C. DE LANGE (2) did indeed find parasites in the cerebral-tissue at the time, which has been confirmed by WOLF, COWEN and PAIGE (5).

DE LANGE's case: From the first few weeks after birth, a girl has revealed cerebral symptoms: poikilothermy, irregular breathing and drowsiness. The ventricular fluid contained a very high protein content. The size of the head increased rapidly, the child dying at the age of 3½ months of pneumonia.

When a post-mortem was conducted, besides pneumonia and exudate in the peritoneal-cavity, extensive inflammatory symptoms were observed in the brain and in the meninges. Both corpora striata and thalami were almost completely necrotic. There was an inflammatory block of the aquaeductus Sylvii and in many places there were hemorrhages and perivascular infiltrations present. In the necrotic lesions there was considerable calcification and infiltration.

The presence of toxoplasmas in pretty well all inflammatory lesions stamps the chronic-necrotizing granulomatous inflammation in the brain of the child as a toxoplasmic encephalitis. DE LANGE states that the fundus oculi was normal at the age of 5 weeks. A microscopical examination of the bulbi was not made.

Shortly after this statement made by DE LANGE, the report on the second case observed in the Netherlands of toxoplasmic encephalitis appeared. Vos had once more made a study of a case he had considered remarkable for some years already and had encountered toxoplasmas in it.

Vos's case : Since the second week after birth there have been increasing symptoms of a meningo-encephalomyelitis : convulsions, vomitus, daziness and a paresis of the left half of the face. The fontanel was decidedly taut. The right lateral ventricle is considerably enlarged, while the left lateral ventricle is not to be punctured. Except for a positive Nonne reaction, there are no abnormalities in the cerebro-spinal fluid. Hydrocephalus gradually develops. A bilateral enophthalmy is the only abnormality mentioned about the eyes.

The child dies at the age of 5 weeks. Abnormalities in the brain were found during autopsy. There are scattered greyish-red lesions of varying sizes present. Microscopically these lesions consist of a chronic-necrotizing inflammation. There is some calcification in the lesions. In the vicinity of these lesions there are numerous smaller peri-vascular inflammatory lesions. Local leptomeningitis is present.

As a consequence of the war this statement made by Vos, which has been exclusively published in Dutch, has not found its way as yet into world-literature. It is a very interesting observation with a very characteristic clinical and histo-pathological picture. It is a pity that apparently no further attention has been paid to the eyes. That the infection arose prenatally in this case, Vos thinks is to be inferred from the presence of calcium-salts in the necrotic lesions.

It is worth mentioning that the mother showed symptoms of diabetes insipidus, which was thought necessary to revert to a restricted encephalitis !

In 1942 Wolf, Cowen and Paige (5) mentioned 2 more cases of fatal infantile toxoplasmosis, toxoplasmas being present in the inflammatory lesions.

The first case is a very fine demonstration of the prenatal inception of the disease.

Case B. R. (Wolf, Cowen and Paige) : Even in utero there was hydrocephalus, in which craniotomy was necessary at delivery. On a histopathological examination being held, an advanced toxoplasmic encephalomyelitis with extensive calcification of the lesions and associated chorioretinitis appeared to be present.

Wolf, Cowen and Paige found toxoplasmas in the central nervous-system, but also in the heart, in the striated muscles and in the adrenals. In all these organs there were inflammatory lesions of the same nature as in experimental toxoplasmosis. Wolf, Cowen and Paige deemed it very probable that this case is an instance of toxoplasma-infection.

Case A. M. F. (Wolf, Cowen and Paige) : A prematurely-born girl reveals symptoms of pulmonary infection on her second day. On the 3rd day circulation troubles make their appearance and the child dies. The eyes were not examined either previous to or after death.

A post-mortem examination showed interstitial pneumonia, acute diffuse myocarditis, encephalomyelitis with focal necrosis and miliary granulomata and finally inflammatory lesions in the adrenals and ovaries.

Although in this case, too, the typical localization in the central nervous-system was not wanting, lesions also occurred in many other organs. Both in the central nervous-system and in the other organs mentioned, toxoplasmas were found in the inflammatory lesions, but also in the glandula thyreoidea, striped muscle tissue and adipose-tissue toxoplasmas were present without inflammatory reaction.

In the following case WOLF, COWEN and PAIGE (6) observed toxoplasmas in the sediment of the ventricular fluid.

Case P. D. (WOLF, COWEN and PAIGE): A white girl, 3 years 9 months of age, was admitted to the hospital because of „epileptic fits", which had started in infancy. Her eyesight was said to have been poor from birth. In early life there were vomiting, difficulty in sucking and swallowing and frequent refusal of food. Coincident with the onset of convulsions, at 5 months of age, strabismus of the left eye was noted. Generalized epileptic seizures occurred every few months, tending to decrease in frequency as the child grew older. At the age of 3 years small areas of intracerebral calcification were first observed by röntgenographic examination. At 3½ years of age ventriculographic studies disclosed pronounced internal hydrocephalus, thought to be the result of obstruction of the aqueduct of Sylvius. The eye-grounds contained focal areas of scarring and pigmentation bilaterally, resulting from old chorioretinitis. The cerebrospinal fluid was xanthochromic and showed a variable degree of pleocytosis. Episodes of increased intracranial pressure associated with drowsiness occurred from time to time. The child remained mentally retarded, and speech was noticeably defective.

The toxoplasma neutralization test with the serum of the child was positive.

In 1944 ZUELZER described three cases of infantile toxoplasmosis. Mention is made here for the first time of toxoplasmosis in a monozygotic twin (case H. and case L.H.). The fact in itself, let alone other arguments, is indicative of prenatal infection.

Case R. S. (ZUELZER): Some days after birth the child is apathetic and occasionally cyanotic. It has convulsions on the eighth day. The fundi oculi were not examined. The cerebro-spinal fluid was xanthochromic, containing 17 cells per mm^3; Pandy's reaction was positive. A further examination yielded no more facts worth mentioning.

The child died at the age of 11 days. On an autopsy being held it was found that the right eye „barely could be visualized", but the left eye was normal in size. The eyes however, were not histologically examined. In many organs focal inflammatory lesions were encountered, viz.: in the brain, spinal cord, myocard, striped muscle-tissue, adrenals, pancreas, testicles, kidneys and lungs. Parasites resembling toxoplasma were found in the brain, spinal cord, skeletal muscles, kidneys, testicles, adrenals and lungs.

Evidently no diagnosis was made during life-time. Although we can speak of a systemic infection of many organs here, too, a disseminated focal encephalomyelitis was dominant. The symptoms of the central nervous-system stood in the foreground also during life and were the cause of death.

After the discovery of parasites, ZUELZER attempted to get confirmation of the intra-uterine character of the infection by examining the blood of the mother. Neither parasites nor toxoplasma neutralizing anti-bodies, however, were found in it. Basing his opinion on this negative result and on the fact that the inflammatory changes were all very fresh, ZUELZER supposed that post-natal infection had taken place in this case. The mention of an abnormality of one of the eyes is important but no further attention was paid to it.

Both the other cases relate to a premature monozygotic twin. Only one of the children was subjected to an autopsy.

Case H. (ZUELZER): The symptoms revealed by this child consisted for the most part of a gradually increasing obstructive jaundice, a swelling of the abdomen, together with a transient fine punctuate rash over the whole body, defective regulation of the temperature of the body, irregular respiration and attacks of cyanosis. Death came during one of these attacks, when the child was one month old.

No examination of the eyes is mentioned when the child was alive. During a post-mortem examination, however, one of the eyes was examined microscopically. There appeared to be iridocyclitis and central chorioretinitis. In the brain there was an intense, internal hydrocephalus and an extensive focal necrotizing granulomatous inflammation with calcification and the formation of cavities in the brain. There was a mild focal myocarditis and myositis. The liver was degenerated to an advanced degree and the spleen was enlarged. Parasites with the morphologic characteristics of toxoplasmas in cyst-like aggregates were found in the brain, spinal-cord, and eye, not in any other organ. Attempts to infect mice with an emulsion of the brain-tissue proved unsuccessful.

Although transmission to mice was not successful, yet ZUELZER did obtain confirmation of the diagnosis of toxoplasmosis in another way. The toxoplasma neutralizing anti-body test with the serum of the mother turned out to be decidedly positive as was also the case with the twin-brother.

The last child (case L.H.) showed the typical clinical picture of congenital toxoplasmosis: retardation of mental development, xanthochromic cerebro-spinal fluid with increased content of protein and transient pleocytosis, intra-cranial calcification, mild internal hydrocephalus, bilateral microphthalmy and chorioretinitis. In the cerebro-spinal fluid of this child no toxoplasmas could be found. At the last examination the child was 7 months old.

STEINER and KAUMP witnessed a case of infantile toxoplasmic encephalitis in a child that died when 3 days old and moreover memtioned an unpublished case referred to them by SAILER. The diagnosis was confirmed by a post-mortem examination.

Toxoplasmic encephalitis in a still-born child was then referred to by ADAMS:

Case ADAMS: Gross examination reveals a tiny brain. The cerebral hemispheres show an extreme hydrocephalus. Most of the cortex is represented by a thin membrane. At the posterior part of both basal ganglia there is some white chalky substance. The anterior part of the aqueduct is occluded. White chalky material is floating free in the ventricular fluid. Microscopic study demonstrates the presence of numerous scattered small granulomas.

There are numerous toxoplasmas seen within the phagocytes, as small cysts, as well as many extracellular parasites.

WINKELMAN and MOORE found toxoplasmas in the brain of an infant that lived for three days and during this time exhibited numerous convulsive seizures, pronounced jaundice and fine petechial hemorrhages in the skin.

The first case of toxoplasmosis in Switzerland was recognized by BAMATTER (2, 3). This case is also concerned with a premature twin. One of the children dies 30 days after birth with symptoms of a hemorrhagic enterocolitis, the histological substratum of which appeared to be necrotizing and ulcerating inflammatory lesions in the colon [1]).

The other child dies 26 days after birth.

BAMATTER's case: Two weeks after birth, fever, rigidity of the muscles and convulsions were revealed. The size of the head gradually increased. The cerebro-spinal fluid is xanthochromic, contains a few cells, but a considerably increased protein content (up to 528.2 mgr.%). In the left fundus oculi a large grey lesion is observed in the macular-area. The child dies at the age of 26 days. After death the presence of toxoplasmas in various inflammatory lesions in the brain and in the eye was noted.

In the cerebral cortex there are reddish-brown lesions visible. The lateral-ventricles are dilated and the wall of the ventricles have a granular appearance (ependymitis granularis). In the grey and in the white substance of the brain there are several cavities which do not communicate with the ventricles. Microscopically leptomeningitis was found, a focal necrosis of the cortex, and numerous peri-capillary granulomas. The main zones of necrosis proceed from the ventricular system. Some of the necrotic lesions contain granules of calcium.

The case represents a typical instance of infantile toxoplasmosis.

CALLAHAN, RUSSELL and SMITH looked through the macroscopical and microscopical material of 10.000 autopsies conducted in the Department of Pathology in St. Louis and found in this way 5 cases of infantile toxoplasmosis, which had been unrecognized as such before. These cases had been examined from 1929 to 1941 and were listed under the diagnosis of "chronic meningitis", "syphilitic meningitis", "encephalomalacia with calcification", etc.

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[1]) Toxoplasmas are said to have been encountered in the inflammatory lesions (personal communication).

CALLAHAN, RUSSELL and SMITH found in characteristic lesions in the central nervous-system micro-organisms, which were morphologically identical to toxoplasmas.

They clearly demonstrated by this that toxoplasmosis has long been a not uncommon disease which, however, until shortly has seldom been recognized as such.

Case M. B. (CALLAHAN c.s.): A three-day-old infant, who had been jaundiced since birth and exhibited marked hemorrhagic tendencies manifested by purpuric spots, bleeding from the mouth, navel and rectum, was admitted to the hospital and died on the same day. The clinical diagnosis was hemorrhagic disease of the newborn. At necropsy internal hydrocephalus, focal calcification in the brain, interstitial pneumonia and interstitial myocarditis were the principal lesions. Organisms morphologically identical with toxoplasma were found in the brain, kidney and myocardium.

Although there was a "wide-spread destruction of brain-tissue with gliosis and calcification", a generalized infection was present.

Case B. B. (CALLAHAN c.s.): A seventeen-day-old infant who had been jaundiced since birth was admitted to the hospital because of vomiting. A diagnosis of icterus gravis and internal hydrocephalus was made and the infant was given supportive treatment. He was discharged from the hospital slightly improved.

He was readmitted to the hospital twenty-three days later with convulsive seizures and partial ptosis of the right eye. The pupils were unequal, the left being slightly larger than the right. The left pupil reacted slowly and with small amplitudo to light, the pupil of the right eye reacted normally. The last two days before death the child was "completely blind". The course was progressively worse and despite a bilateral antrotomy the patient died on the thirty-fourth hospital day. At autopsy internal hydrocephalus, encephalomyelitis, bilateral otitis media and interstitial pneumonia were the principal lesions. Toxoplasmas were identified in the sections of brain and the left middle ear.

Case N. L. E. (CALLAHAN c.s.): A white female infant, delivered at full-term, became ill at six weeks of age and developed severe generalized convulsions, diarrhoea and signs of spinal-cord involvement. It was noted that the child had sunken eyes and fixed pupils. The course of the disease was rapid, and terminally signs of respiratory infection became apparent. Autopsy revealed internal hydrocephalus and a widely disseminated encephalomyelitis with foci of necrosis and numerous miliary granulomatous lesions. Many of the lesions had undergone cystic degeneration while others, especially in the cerebral cortex, were calcified. Micro-organisms identified as toxoplasma were found in the granulomatous foci. The autopsy was limited to the head, and the eyes were not examined.

Case G. F. (CALLAHAN c.s.): A seven-week-old white male infant had failed to gain weight since birth and developed a severe upper respiratory infection. A slight internal hydrocephalus was present on admission and the head gradually increased in size. Symptoms of a spinal-cord lesion developed with paralysis of the upper extremities. Incontinence of both bladder and rectum appeared, the respirations became shallow and the patient expired. At autopsy there was marked internal hydrocephalus and

numerous areas of encephalomalacia in the cerebral and temporal lobes which were surrounded by sharp yellow areas. Many of these areas showed fine calcium deposits and were surrounded by glial nodules. This same type of destruction was present in the spinal cord. Micro-organisms identified as toxoplasma were demonstrated in the lesions of the brain and the spinal cord.

Case CALLAHAN c.s.: A white female infant was delivered spontaneously and was cyanotic at birth. Respirations responded weakly to strenuous attempts at resuscitation but periods of apnoea developed which gradually became prolonged and the infant died, three hours after birth. Autopsy revealed a small amount of clotted blood on the falx cerebri and the tentorium cerebelli, with a few scattered areas of subarachnoid hemorrhage. There was slight internal hydrocephalus with focal ulcerations of the ependyma and a greyish-white exudate on the surface. Micro-organisms identified as toxoplasmas were observed in the lesions. Although there was an accompanying bronchopneumonia no organisms were found in the lungs.

The course of the disease and the histopathological changes point to infection in utero in all 5 cases. No particular attention was paid to the eyes in any of these cases. It is, however, possible that at least in some of the cases there was toxoplasmosis of the eye.

The following case was reported by PRATT-THOMAS and CANNON:

PRATT-THOMAS and CANNON's case: From birth onward cyanosis and edema has existed. The liver and the spleen are enlarged. The child died at the age of 5 days. Shortly before death it exhibits cerebral excitation-symptoms (nystagmus, deviation of the eyes, convulsions). At autopsy, characteristic focal lesions with toxoplasmas are found in the brain, spinal-cord, myocard, lungs, adrenals, stomach, diaphragm and pancreas, while toxoplasmas without reaction are also encountered in the liver, bone-marrow, spleen, kidneys, lymph-nodes, thymus and intestinum. The eyes were not examined during life nor at autopsy.

There was, therefore, in this new-born child an acute, disseminated toxoplasma-infection.

We will also mention here the publications of FREUDENBERG and of GASSER and SCHWARZ. FREUDENBERG diagnosed toxoplasma-encephalitis on the ground of typical clinical characteristics. GASSER and SCHWARZ entertained the possibility of infantile toxoplasmosis in their case, but deemed fetal rubeola-infection also feasible. In both cases the discovery of forms in the autopsy-material resembling toxoplasmas gave considerable support to the diagnosis.

FREUDENBERG observed the case of an infant in Switzerland that revealed symptoms even during the first 2 weeks after birth.

Case C. I. (FREUDENBERG): The child shows convulsions, rigidity of the muscles, abnormal reflexes and drowsiness increasing to coma. Several vegetative functions are disturbed which is associated with the localisation of the process in the diencephalon.

There are a disturbance of the water-salt regulation giving rise to edema, disturbed regulation of temperature (poikilothermy), vaso-motoric disturbances and lability of

the blood-sugar regulation. The cerebro-spinal fluid is xanthochromic, there is a moderate pleo-cytosis accompanied by a marked increase in the content of protein (as much as 1390 mgr.%). The colloid curves show the parenchymtype. The tryptophan-reaction is decidedly positive (which the author puts down to intensive disintegration of the brain). The sedimentation of the erythrocytes has accelerated. A regular checking up on the fundus oculi was made. At the age of 3 weeks the fundus was still quite normal. At the age of 7 weeks, however, there appeared to be a bilateral extensive chorioretinitis (BRUCKNER).

The child dies at the age of $3\frac{3}{4}$ months. There is an internal and external hydrocephalus and a considerable reduction of the brain tissue. The tissue of the brain proved to contain small calcium-deposits, which were not visible during life, on a post-mortem X-ray examination being held. At the time of the provisional publication of the case, the microscopical examination of the brain and eyes was not concluded.

Toxoplasma-encephalitis was diagnosed here on the ground of the clinical picture. The development of the bilateral, extensive and severe chorioretinitis in the course of the disease was of great importance both to the pediatrist and the ophthalmologist in making this hypothetical diagnosis.

Although several attempts were made, toxoplasmas could not be found in the cerebro-spinal fluid during life, neither by direct examination nor by inoculation of laboratory-animals. Microscopical study, however, of sections of the brain and of the eyes revealed the presence of toxoplasma-like micro-organisms (WERTHEMANN).

GASSER and SCHWARZ described their case as "fetal malformations with abnormal calcifications as a consequence of intra-uterine infection".

GASSER and SCHWARZ's case : The mother of an eight-month-old suckling had "German measles" during the third month of pregnancy. The child's mental and physical development from birth onward was defective. There is a mild microcephalus present. At ventriculography an enormous internal hydrocephalus is found to exist, while the remnants of the frontal brain-tissue are intensely infiltrated with calcium. A transient and slight pleocytosis was found in the cerebro-spinal fluid, but a considerable increase in protein. The gold-sol test is of the parenchyma type. There are monocytoid cells with calcium granules in the sediment. Eosinophilia predominates in the blood and marrow, the calcium content of the blood is normal, the fatty-acid has increased. The spleen is enlarged.

Both eyes are greatly "malformed". There is pronounced microphthalmy and enophthalmy on both sides. Further mention is made of "cataracta congenita", the presence of synechiae posteriores and iris bombans.

The child succumbed at the age of 11 months. There was internal hydrocephalus with enormous reduction of the brain-tissue and a chronic, focal encephalitis with lymphocytic infiltration, necrosis, calcification and the formation of granulation tissue. The meninges were only inflamed near the encephalitic lesions. Calcification was also encountered in the liver without being accompanied by inflammatory symptoms. GASSER and SCHWARZ found chronic chorioretinitis in both eyes.

GASSER and SCHWARZ came to the conclusion that an intra-uterine virus-infection, possibly with the rubeola-virus, must have been the cause, although they also had congenital toxoplasmosis in mind. It is not by any means certain, however, that the exanthematous disease of the mother during pregnancy was rubeola ; the diagnosis was never made with any degree of certainty, the woman had not even been under medical observation. On the other hand, we know that toxoplasma-infection in adults may be accompanied by exanthema (PINKERTON and HENDERSON). That the parasitological examination of the cerebro-spinal fluid was a negative one, need not be surprising when we think of the experiences in other cases of infantile toxoplasmosis.

Inflammatory lesions as described in this case in the choroid membrane and in the retina as a consequence of intra-uterine rubeola-infection are unknown to us, but we do know them in the case of congenital toxoplasma-infection. The cataractous changes of the lens with calcification of the anterior lens-capsule accompanied by adhesions of the iris to the lens-capsule strongly bears the characteristics of a cataracta complicata. Even if the fundus oculi could not be examined during life just on account of the cataractous lenses, the inflammatory changes in the anterior bulbus-segment make us suspect beforehand extensive processes are present in the posterior segment in this case, too.

The clinical picture and the ocular abnormalities in particular very strongly suggest, that in this case we are concerned with a case of toxoplasmosis [1]).

The number of publications on the occurrence of toxoplasmosis in man are continually growing.

BOESEN mentions a case of congenital toxoplasmosis in Norway.

DEKKING alludes to a case of congenital toxoplasmosis with bilateral fundus lesions in which the diagnosis was confirmed by autopsy.

B. IN CHILDHOOD

1. TRANSMISSION OF THE INFECTION TO ANIMALS

Two cases of acquired toxoplasmic-encephalitis in older children were described by SABIN (2) in 1941.

One of the cases was fatal and toxoplasma-like structures were

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[1]) BAMATTER, who had an opportunity of studying the microscopical slides of this case, succeeded in demonstrating toxoplasmas. (BAMATTER (3)).

found microscopically in the tissues. Moreover the infection was transmitted to laboratory-animals by means of inoculation of an emulsion of the brain-tissue.

In the other case toxoplasmosis was observed in laboratory-animals inoculated with the cerebro-spinal fluid of the child. The animal experiment in the second case was such that SABIN's conclusion could only be that "toxoplasmic etiology in this case was presumptive".

Case R. H. (SABIN) : A six-year-old boy falls ill with the symptoms of headache, vomiting, weakness in one leg and in the arms and generalized convulsions. Some days before this he had had a knock on the head with a base-ball. At first there were no abnormalities to be observed other than generalized lymphadenopathy and a palpable spleen. Neither are there any neurological abnormalities present. The fundi oculi are normal. Death takes place 30 days after the commencement of the disease under increasing symptoms of encephalitis, state of delirium, drowsiness, occasional convulsions and muscle twitchings over the whole body, irregular respiration, irregular pulse, and high temperatures. Among other things, a varying content of cells and a high percentage of protein were found.

It was striking, says SABIN, how the brain showed no macroscopical changes at all and only very few microscopical ones, and there were but few inflammatory lesions scattered throughout the whole brain-substance consisting of necrosis and cellular infiltration in connection with the blood-vessels. The leptomeninges were thickened in the vicinity of the encephalitic lesions. Other organs could not be examined. SABIN found toxoplasma-like structures in only a few of the inflammatory lesions.

Hence the macroscopical and microscopical picture of the brain differed very considerably from the extensive changes in congenital toxoplasma encephalitis.

In a large percentage of mice, inoculated intra-cerebrally and intra-peritoneally with a brain-emulsion, a typical experimental toxoplasmosis arose, which by sub-inoculation not only could be transmitted to other mice, but also to various other species of animals. The toxoplasma strain isolated by SABIN in this way is known as the "R.H.-strain of human toxoplasma".

The blood taken from the patient after death turned out to contain toxoplasma-neutralizing anti-bodies.

Case W. B. D. (SABIN) : An eight-year-old boy was likewise ill with the symptoms of encephalitis, headache, vomiting, generalized convulsions with deviation of the eyes and nystagmus, cyanosis, twitching movements of muscles, confusion and stupor. There is fever and enlargement of the lymph-nodes. There are no neurological abnormalities. The fundi oculi are normal. The number of cells and the protein content of the cerebro-spinal fluid have increased. Leukocytosis prevails in the blood.

After eight days there was a change for the better ending in complete recovery.

SABIN inoculated some mice and guinea-pigs with the cerebro-spinal fluid from this boy. None of the mice died during the first 5 weeks

and the animals were not further examined. Both guinea-pigs died and toxoplasmas were isolated. Because of the lack of virulence for mice and on account of the fact that spontaneous toxoplasmosis occurs in guinea-pigs, SABIN does not think there is conclusive proof of the toxoplasmas having been isolated from the spinal fluid of the patient.

The fact that SABIN found no spontaneous toxoplasmosis in a large number of the guinea-pigs of his stock and that both inoculated guinea-pigs died on the same day does speak in its favour, however.

The toxoplasma-strain, known as the "W.B.D.-strain", was found to be immunologically identical to the "R.H.-strain" and to a toxoplasma-strain of animal origin.

The toxoplasma neutralizing anti-body test with the blood of the patient, 10 weeks after the commencement of the sickness was negative.

2. MORPHOLOGICAL IDENTIFICATION OF „TOXOPLASMA-LIKE STRUCTURES"

A very significant observation was mentioned by TOMLINSON in 1945 from Panama. In a post-mortem examination on a 10-year-old girl, who had died of sickle cell anemia, TOMLINSON found protozoa, resembling toxoplasma in the brain and in the myocardium without there being any reaction in the surrounding tissue. TOMLINSON points out that this observation was of great significance in accounting for the transmission of the infection by apparently healthy mothers to their children and that this was the first case known to him of "chronic asymptomatic human toxoplasmosis". The occurrence of suchlike infections in man was predicted by WEINMAN (1) after he had observed the existance of "chronic or carrier toxoplasmosis" in mice cured of acute infection.

ROBINSON mentions a case of acute toxoplasmic meningo-encephalitis and chorioretinitis in a 9-year-old girl in a Relief Camp in Italy. He found toxoplasmas in the spinal fluid. The child recovered.

ROBINSON's case: A 9-year-old girl fell acutely ill with headache and high fever. Ten days after the commencement of the illness, various neurological disturbances are found: strabismus, nystagmus, abnormal reflexes and a positive Kernig-symptom. Chorioretinitis is present, too, but particulars of this are not given. The spinal fluid contains both free and encysted toxoplasmas.

The child was treated with sulfathiazole and emetine for 12 days, after which a clinical cure was effected. Nine days after this treatment was terminated the temperature rises again, however, and some neurological disturbances make their appearance. After resuming the sulfathiazole and emetine treatment for 6 days, a permanent cure was effected. Strabismus and nystagmus disappear after some weeks and the chorioretinitis was reported as cured after four weeks from the commencement of the disease.

C. IN ADULTS

1. TRANSMISSION OF THE INFECTION TO ANIMALS

In 1941 PINKERTON and HENDERSON mentioned 2 cases of adult toxoplasmosis. They witnessed two fatal cases of an „acute febrile exanthematous disease with pulmonary involvement".

Case 1. PINKERTON and HENDERSON: A man of 50 years fell acutely ill with fever, diarrhoea and coughing. Some days after the commencement of the disease he developped a maculopapular exanthema all over the body except on the palms of the hands, soles of the feet and face. At a physical and röntgenological examination it appears there are diffuse abnormalities in the lungs: lung-markings throughout both lung-fields, with areas of increased density. Electro-cardiography indicates an infection of the myocardium. No specific abnormalities come to light in the laboratory examinations. The patient dies after a 10-day-illness. The brain was not examined. Abnormalities were found in many organs: interstitial pneumonia, cellular infiltrations in the heart, focal necrosis in the liver and spleen, and perivascular infiltrations in the skin.

Case 2. PINKERTON and HENDERSON: A 42-year-old woman fell ill with the same symptoms as described in the first case. The disease develops in about the same way, only sub finem vitae reflex-abnormalities appear. At autopsy an interstitial pneumonia is found, further necrosis in the heart, in the spleen and in the liver, and peri-capillary infiltrations in the brain with mild inflammatory-reaction of the meninges.

The disease manifests a great resemblance to the Rickettsia diseases. In both cases there was a history of tick-bites. No evidence for the diagnosis of Rickettsiosis was obtained, however, neither by biopsy of the skin, nor by microscopical post-mortem examination, nor by animal-experiments.

The most important microscopical feature in both cases was the presence in the tissues of intra-cellular protozoa having the morphological characteristic of toxoplasma.

These were found in both cases in the inflammatory lesions of the spleen, in the heart and in the lungs, in the second case, moreover, in the brain. In the lungs occasionally alveolar lining cells as well as macrophages lying free in the alveoli and bronchioles were distended with these organisms.

By injecting the blood of the first patient into the peritoneal cavity of two guinea-pigs one of the guinea-pigs sickened and the other died. As toxoplasmosis had not been thought of at the time, the animals were not examined for this. There is, therefore, only presumptive evidence of toxoplasmic-infection in these animals.

The blood of the second patient, however, caused in both of the injected guinea-pigs, a generalized toxoplasmosis, which was transmitted serially. The same lesions were found in the organs of the guinea-

pigs as in the patient and toxoplasmas occurred in all the lesions. "Conclusive evidence for the transmission of the toxoplasmosis to guinea-pigs was thus obtained". The autopsy-material also proved to be infectious to mice. In one of the 2 cases at least, therefore, there was no doubt that the symptoms described were caused by toxoplasmic-infection, which in adults apparently may give a clinical and histo-pathological picture differing wholly from that in infants.

A chance discovery was made by SYVERTON and SLAVIN:

Case M. B. (SYVERTON and SLAVIN): A 65-year-old man has fever, diarrhoea, nausea, cramp in the abdomen, and pains in the right elbow. The patient's physician stated that small macules resembling "rose spots" had been present over the trunk during the second week of illness. He is said to have had a similar illness 24 years ago, which was diagnosed at the time as "typhoid fever". The liver proved to be enlarged. The eye-ground is normal. The repeated demonstration of eosinophilia (26—45 %) was the salient finding in routine laboratory examination. The eosinophilia continued to exist for more than a year.

The patient completely recovered 7 weeks after the commencement of the sickness.

Since the authors suspected trichinosis on account of the pronounced eosinophilia, they performed a biopsy of the musculus gastrocnemius and happened to discover toxoplasma-like protozoa, accompanied by chronic inflammatory changes. They also inoculated mice, guinea-pigs and rabbits with muscle-tissue. Although the animals did not sicken, SYVERTON and SLAVIN found "toxoplasmas" in the kidneys of one guinea-pig and one rabbit of the first passage and in one guinea-pig of the third passage.

Although evidence of toxoplasmosis was found only in 3 of 102 animals in several passages, SYVERTON and SLAVIN deem it a proof of the presence of toxoplasmosis in the patient.

They consider their toxoplasma-strain but slightly pathogenic in view of their experience with the laboratory animals and the survival of the patient. Serial transmission was not capable of increasing the virulence of the toxoplasmas.

SABIN, who examined the serum of the patient 7 weeks after the commencement of the sickness, found no toxoplasma neutralizing anti-bodies.

SYVERTON and SLAVIN consider it possible that the toxoplasmas in this case are not the cause of the disease; they are of opinion that they have discovered a clinical inapparent infection („carrier state").

2. MORPHOLOGICAL IDENTIFICATION OF "TOXOPLASMA-LIKE STRUCTURES"

In 1929 COULON described "parasitic forms" in the cerebro-spinal fluid of a 17-year-old boy in Corsica, who died of meningitis.

COULON's case: A boy of seventeen, living in a small village in Corsica, died after an acute illness of three days duration, characterized by fever and meningeal symptoms. The right eye was large, hard, reddened and immobile. This was thought to be due to intra-cranial sinus thrombosis.

On account of the likeness to encephalitozoon cuniculi and encephalitozoon Chagasi, COULON termed the parasites "encephalitozoon brumpti", although he himself emphasized the fact that the identification of the parasites without further data was pretty well impossible. Moreover he was doubtful whether the parasites had any etiological relation to the meningitis. WOLF and COWEN (1) think that COULON's case might be toxoplasmosis, although considerable doubt continues to exist, especially because no autopsy was done in this case and the histopathological changes in the central nervous system are unknown.

PINKERTON and WEINMAN encountered a fatal generalized infection with a protozoan parasite in an adult in Peru in 1937. They carefully re-studied the morphological and histological features of the case and in 1940 gave their conclusion that the organism in question was toxoplasma.

PINKERTON and WEINMAN's case: A 22-year-old man complained of acute weakness and had fever. Blood films showed a moderately heavy infection of the erythrocytes with Bartonella bacilliformis. The man died after an illness of 12 days duration. Three days before death Bartonellas had almost disappeared from the blood, but in spite of this fact the patient failed rapidly. Necropsy was done. Lesions were found in the central nervous system, myocard, liver, spleen, skin, lymphnodes, lungs, bone-marrow, adrenals and kidneys. In most of the organs focal necrotic and inflammatory lesions were present. In the brain only rare focal collections of cells were present. In all lesions parasites were found.

It is possible that the Bartonella infection activated a latent toxoplasma-infection, which was ultimately the cause of death.

GUIMARÃES describes predominating neurotropic toxoplasmosis in an 18-year-old Brazilian negro.

GUIMARÃES's case: Death occurred after a sickness of 37 days with cerebral symptoms (fever, paresis of the legs, stiff neck, dysphasia, headache). At autopsy a meningo-encephalomyelitis is found, characterized by "extensive inflammatory areas with and without necrosis, spread over both the white and grey substances" and "miliary and sub-miliary granulomas which are generally met with ranged in relation to blood-vessels". Further inflammatory or necrotic foci were encountered in myocard, liver, pituitary gland and lungs.

GUIMARÃES met with toxoplasma-like parasites in the brain and in the myocard.

KEAN and GROCOTT (1) made a similar discovery to that of TOMLINSON and SYVERTON and SLAVIN, this time in a 48-year-old woman. This woman died of "coronary occlusion". The exact diagnosis could not be made

at autopsy either. Among others, myocarditis, foci of encephalomalacia, thyroiditis, thymus hemorrhages and perisplenitis were encountered. In the myocard KEAN and GROCOTT found protozoa resembling both sarcocysts and toxoplasmas. They express the opinion that various cases known in the literature as sarcosporidiosis might be toxoplasma-infection, as PINKERTON and WEINMAN determined in the case described by HERTIG.

PLAUT, too, has by chance found protozoan parasites in the myocard of a 14-year-old boy and a 66-year-old woman. Around the parasites there was no inflammatory reaction. It was not possible to identify the parasites. They bore a likeness to sarcosporidia and to toxoplasma.

The 14-year-old boy died of a sub-acute yellow atrophy of the liver, the 66-year-old woman of an abdominal operation. PLAUT thinks he is concerned here with "human toxoplasma carriers".

II. POSITIVE SERUM TESTS FOR TOXOPLASMOSIS

1. DEMONSTRATION OF COMPLEMENT-FIXING ANTI-BODIES

Only once a case of (infantile) toxoplasmosis is mentioned, in which the diagnosis was exclusively based on a positive complement-fixing test (LEVIN and MOORE).

LEVIN and MOORE's case: A suckling manifests various symptoms characteristic of infantile toxoplasmosis: mental retardation, convulsions, mild microcephalus, intra-cerebral calcification and bilateral chorioretinitis. The microcephalus was already present at birth. The intra-cerebral calcification was discovered at the age of 3½ months. The chorioretinitis was observed at the age of 5 months and was already in an inactive stage. From this LEVIN and MOORE concluded that fetal infection had taken place.

At first it was thought to be tetany and later on cerebral calcification epilepsy (GEYELIN and PENFIELD), but when the chorioretinitis was noted a disseminated infection was surmised, possibly a congenital toxoplasma-infection.

SABIN examined the blood when the child was 1½ years old. He found no toxoplasma neutralizing anti-bodies in the serum of the child nor in that of the mother, but he did find specific complement-fixing anti-bodies in both. SABIN stated that as far as is known, the complement-fixing test is indeed specific, but in this case, he dared not, without further evidence, accept toxoplasma-infection. The complement-fixing test proved invariably to be less susceptible than the toxoplasma neutralizing anti-body test. He mostly found toxoplasma neutralizing anti-bodies, but no complement-fixing anti-bodies.

2. DEMONSTRATION OF TOXOPLASMA NEUTRALIZING ANTI-BODIES

After the discovery of toxoplasma neutralizing anti-bodies in the blood of convalescent monkeys inoculated with toxoplasma (1937, SABIN and OLITSKY), followed the discovery of toxoplasma neutralizing anti-bodies in human serum, a discovery, which was to have great value to the diagnosis of toxoplasmosis in man (1941, SABIN (2)).

SABIN (2) made mention of two cases of toxoplasma-encephalitis in children, 6 and 8 years respectively. The first child succumbed after a month's illness. Inoculation of mice with brain-tissue of this child resulted in toxoplasmosis in the animals. While diagnosis of toxoplasmosis was confirmed in this way, SABIN demonstrated the existence of toxoplasma neutralizing anti-bodies in the blood.

On the other hand, SABIN found no toxoplasma neutralizing anti-bodies in the serum of 15 persons taken at random.

The serum of the second patient described by SABIN appeared to contain no anti-bodies 10 weeks after the commencement of the sickness. SABIN concluded from this — proved later to be wrong — that only a few weeks after the outbreak of the disease the toxoplasma neutralizing anti-body test had any significance in diagnosing.

WOLF, COWEN and PAIGE (4) examined the serum of the mothers of two children, who had died from congenital toxoplasmosis. In both cases the diagnosis was confirmed by autopsy. In the sera of the two quite healthy mothers they found toxoplasma neutralizing anti-bodies. WOLF, COWEN and PAIGE demonstrated by this the existance of clinically inapparent toxoplasma-infection. This was at the same time a proof of their theory that the infection can be acquired by the child during the intra-uterine development from a latent infected mother, and that the so-called infantile form of the disease may be congenital.

Later on WOLF, COWEN and PAIGE (6) described the occurrence of toxoplasma neutralizing anti-bodies in six patients at the ages of 8 months to 11 years with various symptoms of infantile toxoplasmosis and moreover in two of the mothers of these children. All these 6 patients had chorioretinitis, which they with KOCH have described in a separate article (KOCH, WOLF, COWEN and PAIGE).

In two of the six cases the diagnosis was confirmed by the presence of toxoplasma in the cerebro-spinal fluid (case P.D. and case J.F.).

WOLF, COWEN and PAIGE are the first to make the diagnosis of infantile toxoplasmic-infection solely on the ground of clinical symptoms and a positive neutralization test.

The salient points of the last four cases are :

Case A. I. (WOLF, COWEN and PAIGE) : A white boy of 2 years, born one month prematurely, was jaundiced on the fourth day of life and had a diffuse maculo-papular rash, which lasted until the fourth week. At this time the liver and spleen became palpable. When the infant was 7 weeks old, röntgenographic examination of the skull revealed many small, irregular areas of calcification in the brain bilaterally. The icterus disappeared, and moderate anemia and leukocytosis improved after transfusion. At the age of 5 months it was observed that the head was smaller than normal, and in the ensuing months the microcephalus became more obvious. The patient did not learn to talk. At the age of 2 years ophthalmologic examination showed that vision was poor, consisting only of appreciation of moving objects and light perception. There was an alternating convergent strabismus. The fundi showed multiple focal areas of healed chorioretinitis with pigmentation. Mental development was retarded. The liver and spleen were barely palpable at this time. The multiple foci of intra-cerebral calcification persisted. There were no convulsions or focal neurological signs. The patient's blood contained neutralizing anti-bodies to toxoplasma, while the mother's blood proved negative.

Case M. B. (WOLF, COWEN and PAIGE) : A girl aged 4 years was admitted to the hospital with internal squint of the left eye. The strabismus was first noted in early infancy, before the age of 2 months, and persisted. The child's physical status appeared to be normal, but her speech was unsatisfactory, and at the age of 4 years it was more limited than that of her sister, younger by a year. Examination of the eyes showed, in addition to the strabismus, that the left globe was smaller thant he right. Bilateral focal areas of chorioretinitis with black pigmentation occurred in both fundi. Röntgenograms of the skull revealed a number of discrete shadows of calcium density within the cerebrum. The result of an examination of the patient's blood for neutralizing anti-bodies of toxoplasma was classified as positive or suggestively positive. A similar test of the mother's blood yielded a doubtful or negative result.

Case D. H. (WOLF, COWEN and PAIGE) : A negro boy of 11 years had, in his mother's opinion, been normal until the age of 4 years, when there developed external strabismus and pain in the left eye. An ophthalmologist expressed the opinion that the ocular lesions were of prenatal origin. At the age of 7 the boy became subject to frequent petit mal attacks, which recurred at short intervals thereafter. Re-examination of the eyes revealed the presence of an old central chorioretinitis bilaterally. An intelligence test at 10 years and 8 months showed sub-normal intelligence. The general and neurologic examinations showed nothing abnormal except for external strabismus in the left eye and reduced vision in both eyes, particularly the left. Each fundus showed one large central and several smaller, sharply demarcated, chorioretinal lesions. A röntgenogram of the head revealed calcification in the right basal ganglia, and electro-encephalograms disclosed changes associated with the petit mal attacks. The serum of this patient and that of his mother contained neutralizing anti-bodies to toxoplasma.

Case C. J. (WOLF, COWEN and PAIGE) : A white boy 7½ years was brought to the clinic for "trouble with his eyes". At 3 months of age the mother had noticed that the infant did not follow objects with his eyes, that he showed "twitching of the eyes" and that there was an occasional internal squint, especially on the right. In the first year one eye was nearly blind and sight in the other was poor. At 18 months of age the boy had his first convulsive seizure, which was generalized and accompanied by

unconsciousness. Further convulsions occurred at varying intervals during the following years. On neurologic examination at 7½ years of age, the patient was found to walk on a slightly widened base and tended to lose his balance. There was a fine tremor of the arms and some dysmetria on the left. The eyes showed a wandering horizontal and rotatory nystagmus. Central areas of old chorioretinitis were present bilaterally, with smaller peripheral lesions. Röntgenograms of the skull were normal. The electro-encephalogram was diffusely pathologic. The test for neutralizing anti-bodies in the patient's blood proved to be suggestively positive.

SABIN (4) made a serum examination of 151 persons. He examined the serum in 32 cases with symptoms of infantile toxoplasma-encephalitis accompanied by chorioretinitis and without it and also in several mothers of the patients. He found that if :

a. all or many of the symptoms are present (hydrocephalus or microcephalus, convulsions and/or psycho-motoric disturbances and either intracerebral calcification or central chorioretinitis or both) : toxoplasma neutralizing anti-bodies were present to a large extent, both in the child and in the mother, viz. in 10 of 13 patients from 0 to 15 years and in 8 of 10 mothers. The chorioretinitis was macular and the same as that in congenital toxoplasmosis.

b. convulsions and/or psycho-motoric disturbances only were present (no intra-cerebral calcifications, nor chorioretinitis) : toxoplasma neutralizing anti-bodies were rarely present viz. in 1 of 9 patients from 0 to 5 years and in 1 of 2 mothers.

c. only hydro-cephalus or microcephalus (no intracerebral calcifications and no chorioretinitis) were present : toxoplasma neutralizing anti-bodies were not present in any single one of the 10 patients (ages 9 weeks to 5 years) and in 1 of 4 mothers.

Hence one might conclude from this that if intracerebral calcification or chorioretinitis or both are accompanied by symptoms of encephalitis in infancy, the chance that toxoplasma-infection is involved, is very great as well as the chance that the infection has been acquired from the mother in utero.

In several other cases SABIN traced the occurrence of anti-bodies and found them to be present in 2 children of 12 and 14 suffering from encephalo-myelitis resembling toxoplasmosis ; in 3 of 4 mothers of still-born children or children that had died shortly after birth with hydrocephalus or microcephalus ; in 3 of 8 mothers of anencephalic monsters ; in 2 laboratory assistants engaged on toxoplasmas ; in several dealers in rabbits ; and finally in 5 patients from 10 to 69 years old, "with unexplained encephalopathies presenting predominantly severe, persistent headaches, in some associated with hyperostosis frontalis interna".

Finally SABIN estimates that after the exclusion of patients, mothers and the immediate vicinity of patients, 10 % of the population possess toxoplasma neutralizing anti-bodies.

Six cases of "probable toxoplasmic chorioretinitis" have been described by VAIL, STRONG and STEPHENSON. All these 6 patients had toxoplasma neutralizing anti-bodies in the serum, besides three of the mothers. The ages of the patients were between 7 and 23 years. In 5 cases the chorioretinitis was presumably congenital, in 1 case acquired. They made a physical examination of all the patients, in whom, however, no point of contact with any other known etiology was found. In 1 patient intra-cerebral calcifications were found.

A chorioretinitis may, according to VAIL c.s. be the only remnant of congenital toxoplasmosis, which is only discovered when children begin to read.

CROTHERS (1) describes 8 children belonging to 5 families, "in which a clinical diagnosis of toxoplasmic-infection was supported by serologic evidence". In 7 children there was an inactive chorioretinitis together with other symptoms (intra-cerebral calcification in all of them, convulsions in 5, mental retardation in 12, hemiplegia in one child), in one child there was only cerebral calcification present.

In 2 families the symptoms were familiar. In one family chorioretinitis, intra-cerebral calcification and other symptoms (convulsions, hemiplegia, mental retardation) occurred in 2 children. In the other family 2 children had chorioretinitis, intra-cerebral calcification and convulsions, a third child only intra-cerebral calcification. In the last family the mother had intra-cerebral calcification, too.

In one of the mothers the blood was not examined, in the other 4 mothers the toxoplasma neutralization test was positive. In one of the families the blood examination was positive in one of the normal siblings.

In conclusion CROTHERS mentions a child of $7\frac{1}{2}$ months with microphthalmus, hydrocephalus and intra-cerebral calcification. The blood examination of the child is not mentioned, but toxoplasma neutralizing anti-bodies were found in the mother and in 2 older brothers.

WAGENER makes mention of an infant with a unilateral, healed, atrophic, chorioretinal lesion, not localized in the macular region. The child suffered from a congenital hydrocephalus and intra-cerebral calcification. Toxoplasma neutralizing anti-bodies were found in the serum.

In 1945 HEATH and ZUELZER (1, 2) described an interesting obser-

vation in the case of twins. Before a diagnosis could be made, 1 of the twins dies at the age of 1 month. At autopsy focal lesions are found in the brain and in the eye, in which lesions toxoplasmas are present. The other child, who likewise manifested symptoms, was, after this discovery, thoroughly examined. Among other things a bilateral, extensive, chorioretinitis was then found. Toxoplasmas were never encountered in this child. Both the serum of the child and that of the mother, however, were found to contain neutralizing anti-bodies. The blood of the dead child, obtained at autopsy, neutralized very dubiously; this was, however, not examined until some days had passed without any special measures being taken to preserve it.

SCHWARZ and WENDELL demonstrated 2 girls of 5 years:

"The first child had severe pneumonia at the age of 9 weeks, after which most of her symptoms were first noted. The other child had an illness at birth involving the respiratory tract and congenital dislocation of the hips. Both patients had had convulsive seizures earlier in childhood. The clinical observations were essentially similar. Both patients showed mental deficiency. Visual acuity was greatly reduced, and there was ocular nystagmus. Ophthalmic examination revealed white nerve heads and chorioretinitis, involving particularly the macular areas. Pneumencephalograms revealed symmetric dilatation of the ventricular systems. Röntgenograms of the skull in each case showed multiple irregular calcifications distributed throughout both cerebral hemispheres, particularly in the occipitoparietal region".

Toxoplasma neutralizing anti-bodies were found in the blood of one of the patients.

A thorough study and application of the toxoplasma neutralizing anti-body test is mentioned by HEIDELMAN (1945). He examined 211 sera.

HEIDELMAN examined exclusively sera of patients with eye-affections, as well as the parents and a group of normal persons at random.

The first group consisted of 27 patients suffering from a presumably congenital chorioretinitis with the characteristics of the chorioretinitis in infantile toxoplasmosis (ages from 1 month to 25 years). In the 27 persons of this group there is moreover microphthalmus in 6 of them, further there is a very high percentage of nystagmus and strabismus. A thorough physical examination revealed no abnormalities, except in one case, where congenital syphilis was found to be the cause of the chorioretinitis.

Altogether there were anti-bodies present in 17 of the 27 patients, in 6 of the 7 mothers, and in 1 of the 2 fathers. In 5 cases (ages from 1 month to 15 years) with toxoplasma neutralizing anti-bodies, there were besides chorioretinitis other clinical manifestations of toxoplasmosis, viz. in 4 cases intra-cerebral calcifications and in 1 case convulsions and dilatation of the ventricles.

In 4 cases with the symptoms of infantile toxoplasmosis there were no anti-bodies.

The patients of this group may be classified in this way : 18 patients with congenital chorioretinitis exclusively : in 12 of 18 anti-bodies ; 9 patients with chorioretinitis and moreover other symptoms of infantile toxoplasmosis : in 5 of 9 anti-bodies. In 4 cases of chorioretinitis with microphthalmus there were anti-bodies, in 2 cases not.

The second group comprised 97 cases of acquired uveitis (ages from 20 to 57 years) ; in 12 of the 97 cases there are anti-bodies present (in 8 of 59 cases of acquired chorioretinitis, and in 4 of 38 cases of acquired uveitis anterior).

Of 58 normal persons (taken at random) 6 of the 58 had anti-bodies.

Of 20 patients with various other congenital and acquired ocular diseases not one had anti-bodies.

As a conclusion HEIDELMAN says : "Therefore it would appear that the demonstration of neutralizing anti-bodies should be considered a factor of moderate diagnostic value only in patients with congenital chorioretinitis", but also "the absence of neutralizing anti-bodies from serum does not rule out the possibility of toxoplasmic-infection". With a view to this latter, he refers to cases of congenital chorioretinitis combined with other symptoms of congenital toxoplasmosis, in which toxoplasmic-infection was proved, whereas the serum-test was negative (ZUELZER, SABIN (2), SYVERTON and SLAVIN).

HEIDELMAN found anti-bodies in acquired uveitis and in normal persons in 12½ % and 10 % of the cases examined respectively. He tried to account for this in two ways. In the first place by faulty technique and interpretation of the test, which might cause an error of about 10 %. In the second place by assuming that the examined sera might contain unspecific anti-bodies. It did strike him that 5 of the 6 neutralizing sera of the group of normal persons came from negresses on the 10th day post-partum, among which there was one with pre-eclampsia and 3 with puerperal infections. Six other women 10 days post partum, but without infections, were all negative. HEIDELMAN presumed that fever is capable of producing an unspecific neutralization. He did not succeed, however, in demonstrating an unspecific, thermostable anti-body such as SABIN and RUCHMAN found in their "hyperimmune monkey-serum".

RUCKER describes a 52-year-old man in whom a "diffuse choroiditis of low grade" developed, next to abnormal pupil-reactions, "see-saw nystagmus" and tinnitus aurium. The serum showed "slight to moderate neutralization against toxoplasma". RUCKER imputes the

choroiditis and the cerebral symptoms to an inflammatory process caused by toxoplasma.

CALLAHAN wanted to find out the frequency of clinical inapparent and sub-clinical toxoplasmic-infections in St.-Louis. In order to determine this he made a neutralization test on 100 "healthy" persons between 18 and 28 years old consisting of 77 women and 23 men. In the case of 2 single young women aged 18 and 21 years respectively, the test was positive. CALLAHAN points to the fact that in St.-Louis eight fatal cases of toxoplasmosis had been recorded (PINKERTON and HENDERSON, CALLAHAN c.s.).

ADAMS c.s. witnessed a 14-year-old girl with positive neutralization test against toxoplasma and reported extensive investigations of the family of the patient.

Case C. G. (ADAMS c.s.) : The girl had complained of nervous headaches since she was a small child. When she was in the fourth grade at school, the school physician informed the mother that the child had no central vision in the right eye. However the child did very well in school until severe attacks of headaches accompanied by vomiting required her to stay at home. At 12 years of age she first complained of transitory spots before her eyes and began to have occasional pain in the right eye, heard noises in the right ear and suffered from attacks of nosebleeding. She became lethargic.

At the time of admission neurological examination revealed several positive findings. There was a bilateral inactive chorioretinitis and papill-edema on both sides of about 2 diopters. The audiogram showed a slight loss of hearing in the right ear in the low frequencies. There was hyper-activity of the knee and ankle jerks, and a fine tremor in both hands. Röntgenograms of the skull showed evidence of a generalized increase in intra-cranial pressure and one small area of calcification could be seen. The ventriculogram showed a marked hydrocephalus of the lateral ventricles and of the third ventricle, probably caused by an obstructive lesion of the aqueduct of Sylvius.

The mother and 9 of the 10 siblings likewise had a positive neutralization test against toxoplasma. Complete physical, röntgenological and neurological studies, including fundoscopic examination failed to reveal any signs or symptoms of the disease in the mother and in the siblings. One sibling, however, died at birth with an enlarged head. The latter sibling might have suffered from hydrocephaly due to toxoplasmosis occurring in utero (ADAMS c.s.).

ADAMS mentions another 5 cases of infantile toxoplasmosis with positive neutralization test.

In the first case the patient had only one symptom of the disease : hydrocephalus.

Case I. D. (ADAMS) : A 4-month-old male was admitted to the hospital with a three-week-history of rapid increase in the size of the head. The infant was prematurely

born and had several cyanotic attacks in the third week. Encephalography revealed an internal hydrocephaly, no calcifications. The spinal fluid was xanthochromic and showed moderate pleocytosis and increase of the protein content. Fundoscopic examination was negative.

Blood neutralization tests for toxoplasmosis on both the mother and the infant were found to be positive.

There were only convulsions in the case of the following patient :

Case V. R. (ADAMS) : The child was first admitted to the hospital at 4 weeks of age with a history of having had convulsions since 2 days of age. The mother had had a maculo-papular rash on the left arm at the sixth month of pregnancy. This rash left residual spots of pigmentation. Fundoscopic examination was negative as well as the general physical examination. Röntgenograms of the skull were entirely normal.

Blood from both the infant and the mother at this time gave positive neutralization tests for toxoplasmosis.

Afterwards the motor and mental development of the patient appeared to be retarded.

The type of disease in the following patient is very much like that described in adults by PINKERTON and HENDERSON.

Case C. K. (ADAMS) : A 3-year-old female was admitted to the hospital with a three months history of a generalized macular rash resembling measles, joint pains, fluctuant fever, weight loss, anorexia, irritability and anemia. The eyes, including fundoscopic examination, ears, nose, throat and lungs were normal. There was a slight amount of cervical adenopathy present. On the right anterior chest wall there was a small tender sub-cutaneous nodule the size of a small lymph-node which later disappeared. Both liver and spleen seemed enlarged.

The neutralization tests for toxoplasmosis were positive on several different occasions both for the patient and her father but were negative for her mother. The patient's course in the hospital was marked by daily elevations of the temperature to 104° F. or 106° F. and associated with this, a macular rash over most of the body with the exception of the hands and feet.

Case ADAMS : A still-born male infant was delivered after a craniocleisis had been performed because of a massive hydrocephalus. The mother during the eighth month of pregnancy had a generalized maculo-papular rash that lasted three weeks.

Pieces of the brain were saved at the time of the craniocleisis. Some of these were injected intra-cerebrally into mice and guinea-pigs, and histological sections were made of the others. None of the animals injected contracted toxoplasmosis, however microscopic sections of the brain revealed minute areas of calcification and an occasional toxoplasma close to these areas. Blood drawn on the mother post-partum for toxoplasma neutralization was positive.

In the following case, too, there is but one single symptom : chorioretinitis.

Case C. B. (ADAMS) : When 6 months of age the infant had a „roving gaze". The parents state that this was rather insidious in onset. On examination of the fundi a bilateral chorioretinitis was found. The toxoplasma neutralization tests were positive for the mother and the infant, but negative for the father.

In 1946 JOHNSON c.s. gave the result of serum examinations in cases of "choroiditis". They deem the chances very great that toxoplasmic choroiditis, as a sole manifestation of toxoplasmic-infection, is not an uncommon affection. JOHNSON c.s. examined the sera of 32 selected patients with choroiditis and in addition of other members of the family. The sera of 20 patients were positive. These 20 patients were classified by JOHNSON c.s. as follows :

a. 4 patients with probably congenital choroiditis, ages from 3 to 5 years.

b. 16 patients with presumably acquired choroiditis, ages from 15 to 50 years.

All the patients in the first group had intra-cerebral calcifications, in the patients of the second group choroiditis was the only symptom.

If JOHNSON c.s. collected all the cases of choroiditis by toxoplasma from the literature, then it would appear that of 45 patients 7 only had no intracerebral calcifications and that, if the choroiditis only appeared after the 15th year, calcifications were never seen. In 4 cases JOHNSON c.s. also examined the members of the family. They gave the following description of these 4 families :

1) The first child was prematurely born by 2 months ; it is a backward child with bilateral choroiditis, cerebral calcification and toxoplasma neutralizing anti-bodies. The mother and the following 5 children all have anti-bodies. The following 4 children have them alternately, beginning with a negative. The mother has "typical toxoplasmic calcifications" of the brain.

2) The mother has toxoplasma neutralizing anti-bodies. The first child has bilateral congenital choroiditis, cerebral calcifications and is mentally deficient, the second child has anti-bodies, too. During the third month of pregnancy of the first child a "pet puppy" went blind and had convulsions and diarrhoea.

3) The mother has probably congenital, unilateral choroiditis, cerebral calcification and toxoplasma neutralizing anti-bodies.
A 3-year-old daughter has no abnormalities and no anti-bodies. Therefore no infection, nor immunity has been transmitted to the child.

4) A 22-year-old woman suffers from a unilateral, acquired, central choroiditis during the second month of her first pregnancy. After a chance abortus the choroiditis was cured, only to flare up again during the second pregnancy, now also in the other eye. There are anti-bodies against toxoplasma in the serum. The child that was born, was normal (neutralization unknown) and the choroiditis became again inactive. During the third pregnancy the choroiditis became active once more, sulfadiazine had no effect and a therapeutic abortus followed, after which the choroiditis again became inactive. There were no abnormalities in the fetus.

JOHNSON c.s. assume that pseudocysts were activated chemo-hormonally during pregnancy. Hence the patient would probably be suffering from chronic toxoplasmosis activated in three successive pregnancies. JOHNSON c.s. compare this observation with WEINMAN's findings (1)

in chronic toxoplasmosis of mice and with observations they made themselves in a rabbit cured of toxoplasmic-infection. The animals harboured toxoplasmas as pseudo-cysts without there being any signs of an active infection. These pseudocysts, however, could be activated by sub-inoculation.

Two mothers of children with presumably congenital toxoplasmic choroiditis had both anti-bodies, one of these mothers, moreover, had intra-cerebral calcifications.

In one family toxoplasma neutralizing anti-bodies were found in one of the five siblings and in another family in 7 of the 9 siblings. In 2 other families the children of mothers suffering from toxoplasmic choroiditis showed no anti-bodies in the serum, nor any other symptoms.

JOHNSON c.s. examined a case of sympathetic ophthalmia and a case of retinitis exsudativa externa (COATS) without finding any anti-bodies.

In 2 laboratory assistants they found an increasing percentage of anti-bodies in the serum without the appearance of any other symptoms.

One of these two became the mother of a healthy baby.

Finally MILLER mentions the case of a 4-year-old girl. He attributes the symptoms to a probably congenital toxoplasmosis :

> With the exception of a lethargy lasting a few hours after birth, the baby was normal until 2½ months of age when she had diarrhoea. During this illness she had many convulsions. From the age of 2½ years onward she had repeated attacks of convulsive seizures resembling „petit mal". At the age of 4 years the head circumference is slightly below normal, although not definitely microcephalic. The child is mentally retarded, she has a marked lack of speech. X-Ray photos showed a large number of small calcified particles scattered throughout the brain. Ophthalmologic examination showed nystagmus and chorioretinitis.

The toxoplasma neutralization test with the serum of the child and of the mother is reported to be positive.

III. HISTOPATHOLOGICAL AND CLINICAL DESCRIPTIONS SUGGESTIVE OF INFANTILE TOXOPLASMOSIS

Histo-pathological changes as seen in infantile toxoplasmosis have been described on several occasions without a cause being assigned.

RICHTER recalls a case described by WOHLWILL in 1921 of congenital encephalitis by a cause unknown. Indeed there is a strong resemblance in so far as the incompleteness of the description admits

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of this conclusion. There was no longer any chance of re-studying the material for the presence of toxoplasmas.

The same applies to one case described by BRANDT and to two described by FISCHL (1, 2, 3) as so-called "encephalitis congenita VIRCHOW". The latter cases have been brought to the fore by WOLF and COWEN (2).

BAMATTER (3) thinks there is a great likeness to toxoplasmic encephalitis in a case described by MULLER [1]).

The syndrome of clinical symptoms, met with in infantile toxoplasmosis has also attracted attention of late even if the etiology could not be stated.

MERRITT and ARING have noted that the symptoms described by LICHSTEIN and SOLIS-COHEN in a 22-year-old boy and in his father as „Familial tuberous sclerosis (epiloia) without adenoma sebaceum" are possibly due to toxoplasma-encephalitis. KOCH shared this opinion later on.

The symptoms in the 46-year-old father were restricted to epileptic seizures and 1 or 2 small intra-cerebral calcifications on the röntgenogram of the skull. The 22-year-old son was an epileptic from his 2nd year, had decided mental retardation and showed extensive choroidal changes in both eyes. Numerous calcified deposits were seen on the röntgenogram of the skull.

KNAPP mentions the following case:

KNAPP's case: A child is found to be blind shortly after birth. At the age of 10 weeks extensive fundus changes were observed in both eyes. Later on the child developed spasticity in the left leg. It was thought to have good mentality.

At first it was thought to be glioma retinae, afterwards toxoplasmosis.

PFEIFFER considered toxoplasmosis in two cases with chorioretinitis.

RICCI mentions the history of a 13-year-old girl as an instance of a possible infantile toxoplasmosis.

RICCI's case: The child had an acute febrile sickness with convulsions at the age of 21 months. The convulsions were repeated later. Röntgenographic examination of the skull revealed intra-cerebral calcifications and ventriculography showed dilated ventricles. There were quiescent chorioretinal lesions in both fundi.

We ourselves have described two children with remnants of a presumably congenital encephalitis and bilateral chorioretinitis and

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[1]) The presumption of BAMATTER has been confirmed, as toxoplasmas were found at a re-study of the autopsy-material (WERTHEMANN).

deemed toxoplasmosis to be the cause (BINKHORST (2, 3)) (see Part II: Own Observations: cases 16 and 17).

BRÜCKNER mentions the case of a 4-year-old boy, who had a disease of the central nervous-system at the age of 11 months, accompanied by a serious inflammation of the eyes. BRÜCKNER considered toxoplasmic-infection to be the cause.

RYERSON describes a suspected case of toxoplasmic chorioretinitis in a woman of 19 years.

GLANZMANN (1) deems toxoplasmosis to be very probable in 3 children.

Case 1. (GLANZMANN): A child of 14 months has had extra-pyramidal rigidity in the muscles of the limbs and fits of convulsions since the third month. There are an enlargement of one of the lateral ventricles and symptoms of an increased intracranial pressure. There are calcifications in the region of the plexus choroideus. The child is dazed and imbecile. The cerebro-spinal fluid is normal. Ophthalmoscopic examination: there is atrophy on both sides of the optic nerve head and in both macular areas there is a large, old inflammatory lesion.

Case 2. (GLANZMANN): A seven-year-old imbecile girl has microcephalus, intra-cranial calcification, bilateral microphthalmy and enophthalmy. The fundus oculi is not to be evaluated. There are some remarkable skeletal changes: dwarf growth on account of a lack of the enchondral ossification (looked upon by GLANZMANN as a consequence of disturbances of the pituitary gland) and an excessive periosteal ossification of the skull, ribs and diaphyses. The child's growth has been stunted from birth. Three other children in this same family have died with cerebral symptoms at ages varying from 13 months to 3 years. GLANZMANN deems familiar toxoplasmosis probable here.

Case 3. (GLANZMANN): A boy of 4 years shows microcephalus, idiocy, cerebral calcification in the plexus-region and small, old choroiditic lesions in the fundus oculi.

GLANZMANN considers the symptoms in question pathognomonic for toxoplasmosis and views them as remnants of a healed toxoplasma encephalitis.

BRÜCKNER c.s. described 3 cases of "uveitis" in very young children with symptoms of meningo-encephalitis. Ocular manifestations in the child described by FREUDENBERG together with a description of two children, who had been under observation in the Netherlands (see Part II: Own Observations: cases 18 and 19) formed the subject of the publication. We expressed the opinion that toxoplasmic-infection as the cause of these three cases should be the subject of serious consideration [1]).

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[1]) In the meantime the presumption that toxoplasmic-infection was the cause, in the case of C. I. (FREUDENBERG) has been confirmed by a post mortem examination.

It is not improbable that the macular exudate demonstrated by VERHAGE in a case of „poliomyelitis" (which diagnosis was doubted again later on) and the two cases described by P. G. BINKHORST and LORENTZ DE HAAS of central chorioretinitis and encephalitis of unknown etiology have likewise been caused by toxoplasma (BINKHORST (2, 3)). The same applies to many of the so-called macular colobomas described in literature (VAN DER HOEVE and others).

CHAPTER IV

OCULAR MANIFESTATIONS

I. HISTOPATHOLOGY

There are various histopathological descriptions of ocular lesions in man caused by toxoplasma. Altogether there are reports on at least 15 microscopically examined eyes of 9 children.

This number in the still comparatively rarely described disease, points to the significance of the ocular symptoms in the syndrome of infantile toxoplasmosis. Information has been taken from JANKÛ (1923); WOLF and COWEN (1937) (1); WOLF, COWEN and PAIGE (1939 (1) and 1942 (5)); ZUELZER and HEATH (1944—1945); BAMATTER (1947) (3); GASSER and SCHWARZ (1947); KEAN and GROCOTT (1948) (2).

In all these cases we are concerned with fatal infantile toxoplasma-infections giving rise to encephalomyelitis, presumably all of fetal origin. On a microscopical examination parasites resembling toxoplasma were described in nearly all the eyes, only WOLF, COWEN and PAIGE (5) fail to make any special mention of these parasites being found in one case (case B.R.), while JANKÛ does mention parasites in only one of the eyes. Besides this parasitic-morphological confirmation of the diagnosis, the identity of the parasite was confirmed by transmission of the infection to laboratory-animals in two cases (case L. M., WOLF, COWEN and PAIGE (5) and the case of KEAN and GROCOTT (2)).

Here follow briefly the abnormalities of the visual apparatus observed during the life time in each case. In the present stage of our knowledge, we deem it of sufficient importance to give the original descriptions of the histopathological findings as fully as possible. For further data on the various cases, we refer to the preceding chapter.

The very first observation of toxoplasmosis in man, made by JANKÛ in 1923, gave us the first clinical and histopathological description of the ocular lesions. JANKÛ illustrated his article with drawings of the ophthalmoscopical picture of the so-called macular coloboma in both eyes and describes what he observed in the eyes as follows (after WOLF and COWEN (1)):

The left eye was smaller than the right and the ocular movements slow and limited to upward movement. The pupils were regular and reacted to light directly, but poorly consensually. The conjunctiva, sclera, cornea, anterior chamber and media of the posterior chamber of the right eye were normal. The nerve head was vertically oval, blurred, greyish-white in colour, mildly elevated, and its vessels of small calibre. In the position of the macula there was a horizontally oval, distinctly marginated area, 3 × 2 disc diameters in size, having a slightly concave surface. This atrophic zone was bordered by a band of pigmentation which was dark and finely granular. Along the inner margin of the latter there was a yellowish zone which merged into the white of the atrophy proper. In this yellow zone some reddish choroidal vessels were seen. In the papillary half of the lesion there was black pigment interspersed with greyish-white tissue running horizontally and nasally. The retinal vessels were absent in this zone. The rest of the retina showed no obvious abnormalities. The eye was emmetropic.

Left eye : The bulb of the left eye was smaller than the right. The conjunctiva, sclera, cornea and lens were normal. In the nasal third of the eye-ground there were greyish-white reflexes beginning at the extreme periphery and reaching the macular region. Here there was a white area, $2\frac{1}{2} \times 5$ disc diameters in size, bordered by black pigment. The greyish-blue reflex seemed to come from an irregular surface as in severe detachment or tumor of the retina. The atrophic zone in the macular region was considerably depressed in the center, yellowish-white in colour, with reddish streaks near the margins and specks of pigment increasing in number toward the periphery. No retinal vessels were visible in this zone. The papilla was widely elevated and greyish in colour, and the edge nearest the macular lesion was completely obscured. The rest of the eye was normal. The eye was hypermetropic and its tension normal.

The child died at the age of eleven months and both eyes were microscopically examined.

Right eye : Gross : The bulb was normal in size, regularly rounded and presented no external abnormalities.

Microscopic : In the section which reached the edge of the lesion in the macular region at a distance of 3 disc diameters from the papilla, the outer nuclear layer of the retina lost its regularity. Its cells were disseminated for a short distance into the outer molecular layer up to the internal nuclear layer. The outer molecular layer was broadened and the external limiting membrane was interrupted. There was fragmentation of the rods and cones with the production of pale staining granular material into which cells of the outer nuclear layer were dislocated through the disrupted external membrane. The pigmented epithelium formed a continuous band for the most part, although some of the cells were depigmented. The lamina basalis of the choroid was normal. The choroid was congested and the vessels contained large numbers of polymorphonuclear leucocytes and lymphocytes.

Deeper in the macular lesion there was a marked loss of pigment in many of the cells of the pigmented layer of the retina. The underlying choriocapillary layer was converted into a broad mass of connective tissue fibers containing many fibroblasts and small peri-vascular collections of lymphocytes.

Passing further into the lesion the outer and inner nuclear layers of the retina became irregular, impinging on the molecular layer. Here the chorio-capillary layer was completely obliterated and the choroid more vascular and more heavily infiltrated by round cells. The lamina basalis had disappeared and the pigmented layer of the retina was

disrupted for short distances. Extrusion of cells from the outer nuclear layer into the degenerated layer of rods and cones occurred. The retina was densely adherent to the choroid and in places was separated from the pigmented layer.

The defects in the pigmented layer of the retina and lamina basalis of the choroid became more pronounced as the deeper part of the lesion was reached and finally the pigmented layer disappeared completely. Extrusion of parts of the outer nuclear layer into the choroid occurred through this zone. The choriocapillary layer became more markedly infiltrated by lymphocytes with small numbers of polymorphonuclear leucocytes and plasma cells. The infiltration extended into the peri-vascular spaces of the larger of the choroidal vessels.

Where the retina was markedly changed the inner nuclear layer was divided in two by a band of granulation tissue. The external portion curved towards the choroid at the expense of the outer molecular layer. Frequently the islands of disrupted pigmented epithelium hypertrophied, extending into the rest of the retinal tissue, forming large clusters of finely granular, dark brown or black pigment. Through the intervening defects in the pigmented layer and lamina basalis, hyperplastic chorio-capillary layer and intermediate stratum of the choroid proliferated fan-wise into the retina. Such connective tissue trabeculae surrounded the masses of displaced pigmented epithelium. Only small numbers of pigmented retinal cells were displaced in the other direction, into the choroid. Those that were extruded into the rest of the retina reached the internal limiting membrane and disrupted the intervening layers. The inner nuclear and molecular layers and the ganglionic layer were thinned out, showed an increase of glial tissue and were invaded by newly formed connective tissue and pigmented epithelial cells. In the center of the lesion the internal limiting membrane of the retina was destroyed and clumps of hyaline and granular material was present on the internal surface of the retina. The choroid was densely infiltrated with cells such as those described above.

The papilla of the optic nerve was edematous and projected into the interior of the eye. The connective tissue of the optic nerve was increased but its peri-neural space presented no abnormalities.

The histological findings therefore corresponded to the ophthalmoscopic picture of the right eye-ground. The distinctly marked pigmented edge of the macular coloboma represented the hypertrophied pigment layer where it was abruptly interrupted. The yellowish band internal to it probably represented the extruded external retinal layers occasioned by the interruption of the pigmented layer and possibly also by the glial reaction in the external nuclear layer. The accumulations of pigment and fibrous tissue were clearly explained histologically. The pinkish white areas probably were accounted for by the gliosis in the retinal layers and the shining of the sclera through the heavily infiltrated areas in the choroid separating its vessels.

Left eye : Gross findings : The bulb was smaller than the right. On transillumination it showed thinning of the sclera in the macular region which was not the case in the right eye. Sections were prepared as of the other eye.

Microscopic : The author described a congenital malformation of the retina present on the temporal side of the ciliary body. It was a tumorlike hypertrophy of the retina originating in the external nuclear layer and layer of rods and cones, with formation of rosets and without inflammatory changes.

The macular lesion in this eye was in many respects like that in the right eye. It differed in that the inflammatory phenomena in it were fewer, while fibrosis and gliosis were more marked. Near the edges of the lesion there was hypertrophy of the pigmented

layer of the retina with a disappearance of the basal lamina and fibrosis of the chorio-capillary layer. Fibrous tissue from the choroid spread fan-wise through the defects in the pigmented layer into the retina to mix with glial tissue there. Retinal pigment was absent in the heart of the lesion except for a few remaining islands surrounded by fibrous tissue from the choroid. In places pigmented epithelium had hypertrophied extensively and projected into the choroid as well. Glial tissue replaced the layer of rods and cones and the external nuclear and molecular layers at the edges of the lesion, while centrally it replaced all but the ganglionic layer. There were few vessels in this glial tissue. In the chorio-capillary layer, especially near the margins of the lesion, there were mild inflammatory changes, chiefly peri-vascular. In addition there were scattered extraordinarily large round or oval cells. These were markedly vacuolated and had round nuclei with a nucleolus. There was a peri-nuclear halo merging into the finely granular, foamy cytoplasm. They varied from 10 to 15 μ in diameter. The author felt these might have to do with parasites in one stage of development.

Parasitic cysts : The author described these in the right eye but stated they were absent in the left. He referred to them as sporocysts. They were distributed throughout the lesion in the right eye. The majority occurred singly or in pairs in the external molecular layer, but they were also found in the external and internal nuclear and ganglionic layers. The sporocysts were stained most intensely with hematoxylin and eosin and less so by the VAN GIESON and MALLORY stains. There was no reaction of the surrounding tissue to these cysts, the adjacent structures being simply displaced and showing no degenerative changes. In the external molecular layer there was some tendency to concentration of cells which the author took to be glia, about the margins of the cysts. The latter were absent in the choroid and in the central part of the macular lesion where the retinal change was greatest. The greatest distance at which sporocysts were seen away from the macular lesion was in the retina on the nasal side of the papilla. They were absent in all other parts of the eye.

The structure of the sporocyst and its sporozoites lead the author to classify this parasite tentatively as a protozoan of the class of Sporozoa.

Hence both eyes showed among other things inflammatory- and productive changes in the macular region, producing the ophthalmoscopical picture of a coloboma. Sporocysts which the author considered to belong to the protozoa were present in the retinal lesion in the right eye.

The next statement was made by WOLF and COWEN (1), fourteen years after JANKÛ's publication (case J. S.). An ophthalmological examination was made on the 28th day, shortly before the death of the child. Only few notes were made on it (the diagnosis and the significance of the case, it is said, only came to light on a post mortem examination).

"The media of the right eye were clear. Above especially nasally was an elongated area of retina which appeared yellowish-white. Retinal vessels were to be seen on the surface. There were no hemorrhages. This area was about 4 disc diameters in size. Just temporal to this was a zone of choroidal atrophy with pigment clumping about 2 disc diameters in size. The vitreous of the left eye was quite hazy. In the periphery of the upper half of the retina was a yellowish-white area similar to that in the right

eye. There were no new-formed vessels or hemorrhages. It was the consensus of opinion that the elevated areas in the retina were of inflammatory origin. However, glioma of the retina with invasion of the brain was considered a diagnostic possibility."

On the thirtieth day the child died and a post mortem examination was held, which yielded the second histopathological description of ocular lesions caused by toxoplasma:

"Left eye:

The retina and choroid showed no pathological changes except at the site of a large focal area of inflammation corresponding in position to that observed in the ophthalmoscopic examination. In some portions of this lesion the process was very intense, while in the least affected areas, comprising the major portion of the focus, there was intense edema of the retina with only a mild inflammatory reaction, largely confined to the blood-vessel walls. Here there was congestion of the capillaries, about which were small numbers of lymphocytes and plasma cells. Where the process was somewhat more severe, similar cells and occasional eosinophiles and lipoid-laden phagocytes were scattered singly in the loose meshed stratum opticum, ganglionic and inner molecular layers, the last being the least infiltrated. On the free surface of the internal limiting membrane were small numbers of lipoid-laden phagocytes, lymphocytes, large mononuclears, occasional plasma cells and neutrophiles, and amorphous cellular debris. The majority of the nerve cells of the ganglionic layer had disappeared while the few that were recognizable were markedly vacuolated. Parasites, which varied considerably in size were found scattered singly or in small groups in these three retinal layers. In some areas they were very numerous, as many as fifty individual parasites occurring in a single oil immersion field. In other regions there were only scattered parasites, occasional clusters, or a complete absence of organisms. In general the severity of the inflammatory cellular reaction paralleled the degree of infestation, but this was not always the case since the parasites were sometimes seen without evidence of concomitant reaction. Parasitic cysts like those in the central nervous system were also present in these layers.

The inner nuclear, outer molecular, and outer nuclear layers were less edematous than the more internal layers, the edema being most marked in the inner nuclear layer. Inflammatory cells were absent. Parasites, free and encysted, although generally less frequent, were quite numerous in certain foci, chiefly in the outer nuclear layer.

In the layer of rods and cones, small numbers of neutrophiles, monocytes and lymphocytes were encountered. In some places there was degeneration of this layer with replacement of the rods and cones by amorphous hyalinoid material. Small numbers of parasitic cysts and clusters of free parasites were present. The pigment layer occasionally showed disruption of its cells with cytoplasmic vacuolization and freeing of the pigment.

In the most severely involved portions of the inflammatory focus in the retina there was an almost total necrosis of all the retinal elements. In one such zone where the retina was of normal width, only a few cells of the inner nuclear layer survived and the site of the inner molecular and outer nuclear layers was marked by a band of bluish amorphous material. A few cells of the pigment layer also survived. Aside from scattered plasma cells and lymphocytes, there was no infiltration in this region, although occasional parasites were present. In another larger zone of retinal necrosis, this layer was swollen to more than twice its normal width. All that remained of its elements were occasional nuclei of cells of the nuclear layers and amorphous cellular debris. Large numbers

of free parasites, some in mononuclear cells, were seen in this region, more frequently in the internal half of the retina. Many cells of the underlying pigment layer were displaced toward the choroid by the degeneration and edema and some were disrupted and had discharged their pigment.

The chorio-capillary layer of the choroid was congested and the endothelial cells of its capillaries were plump. It was considerably infiltrated by an exudate like that found in the retina. Rare parasites were scattered singly through the exudate, which was heaviest beneath the most severely involved portions of the retina. A similar but less dense exudate was present in some parts of the lamina vasculosa of the choroid, whose arterioles often showed endothelial hyperplasia. Other parts of this coat were edematous but free of inflammation. Rare single parasites were seen in the inner portion of the choroid.

The sclera appeared normal. There was no infiltration of its vessels or nerves. It harboured no parasites.

Optic nerve, intraorbital portion: The dural sheath was normal. The pial and arachnoidal sheaths were moderately infiltrated by monocytes, some of which were lipoid-laden, lymphocytes and plasma cells. The connective tissue septa within the nerve were not thickened and there were no changes of note in the nerve bundles. At a short distance from the bulb the intraorbital portion of the nerve on one side showed an extension of the inflammatory process into the substance of the nerve for almost a third of its width. This was heaviest in the septa and about the blood vessels but diffuse infiltration was also seen. There was no accompanying necrosis and no parasites were observed.

Right eye: A localized inflammatory lesion of the retina and choroid similar to that in the left eye was present in this eye.

Where the process was most severe there was a complete destruction of all layers of the retina with disruption of the pigmented layer and a dispersion of the pigment into the nearby inflammatory tissue of the external layers of the retina. On the internal aspect of this region there was a very loose granulation tissue projecting into the posterior chamber, composed of fibroblasts, hyperplastic capillaries and small numbers of lymphocytes, monocytes, plasma cells, and occasional eosinophiles. In the deeper portions of the necrotic zone, where the retinal architecture was completely obliterated, the exudate became heavier but was similar in its composition. As the choroid was approached it became mingled with the internally displaced masses of extra- and intracellular retinal pigment. Many of the pigmented cells were considerably hypertrophied.

The other findings in the bulb and optic nerve were very much like those in the left eye except for an absence of infiltration of the parenchyma of the nerve. Parasites were present in similar numbers".

Hence there was indeed in both eyes a focal chorioretinitis with necrosis of the retina and disruption of its architecture and dense infiltration of the choroid. The optic nerves showed a similar infiltration in their leptomeningeal sheaths and in the left optic nerve there was a focal infiltration in the optic nerve parenchym itself. Wolf and Cowen concluded that the inflammatory process in the eyes was most marked in the choroid, while the necrosis was restricted to the retina. A protozoan parasite, thought to be the causative agent, was found in the lesions.

The same authors, in conjunction with Beryl Paige (1) observed

shortly afterwards another case of infantile encephalomyelitis, accompanied by ocular symptoms and caused by toxoplasmas (case C. D.).

On the left side there is enophthalmus. Nystagmus and a deviation of the eyes are present. In the fundus oculi there were at first no abnormalities observed, but another examination a few days before death occurred revealed an irregular reddish-brown area in each macular area about 1 disc diameter in size. These changes were interpreted as resulting from hemorrhage associated with multiple injuries of the central nervous system, sustained in the course of delivery.

The child died at the age of 31 days and a post mortem examination was conducted. The posterior hemisphere of one of the eyes was microscopically examined.

"One portion of the retina showed edema of all its layers and distortion of the stratum opticum, ganglionic and inner molecular layers. The capillaries in this zone had undergone endothelial hyperplasia. Many nerve cells in the ganglionic layer were partially degenerated. The layer of rods and cones was markedly necrotic. The pigmented layer was partially disrupted and the destruction of its cells gave rise to much extracellular pigment. The choroid was congested, showed capillary hyperplasia, and was infiltrated by plasma cells, lymphocytes and eosinophils. The leptomeningeal sheath of the optic nerve showed a similar mild infiltration."

The fundus-changes observed, appeared not to be based on a hemorrhage. There was a focal chorioretinitis, while a mild perineuritis was present. Toxoplasmas were met with in the retina and in the choroid membrane.

In 1942 WOLF, COWEN and PAIGE (5) gave the results of a microscopical examination of the eyes in two cases of infantile toxoplasma-encephalitis. In one of the cases at least toxoplasmas were found in the ocular tissues.

WOLF, COWEN and PAIGE made the following remarks on this case (case L. M.) :

On the twelfth day after birth enophthalmus and microphthalmus appeared to be present (the cornea measuring approx. 7 to 8 mm in diameter). There were nystagmoid movements of the eyes. The reaction of the pupils to light was absent. There were a few large bloodvessels visible in the iris. In both eyes membranous masses, apparently vascularized and obscuring the fundi, were seen posterior to the lenses. Pinkish reflexes were obtained through the membranes in the vitreous.

The diagnosis was congenital microphthalmy. One of the following possibilities were entertained : persistant tunica vasculosa lentis, detachment of the retina, retino-blastoma with intracranial complications.

The child died at the age of 9 weeks. In each eye chorioretinitis was present with an outgrowth of partially organized granulation tissue into each vitreous almost to the lenses.

Quoting word for word WOLF, COWEN and PAIGE say of the microscopical examination :

"Chorioretinal lesions were present in each eye. The changes in the retina were essentially of the same necrotizing and inflammatory type as those noted in the brain. There were present edema, congestion, degeneration and disappearance of neural elements, dislocation of portions of the nuclear and hypertrophied pigmented layers, moderate peri-vascular and diffuse infiltration by lymphocytes and plasma cells, varying degrees of astrocytosis and endothelial hyperplasia of capillaries and outgrowth of granulation tissue into the vitreous. This outgrowth of granulation tissue was greater in degree than in the previous cases and formed the large masses observed ophthalmoscopically. The choroid was moderately infiltrated and congested. The sclera appeared normal."

The other child (case B. R.) died at birth. It was observed that the right eye was smaller and that enophthalmus was present. Microscopic observation of the eyes :

"Large patches of chorioretinitis were seen in each eye. The retina was considerably swollen and the changes were fundamentally like those seen in the brain. The necrosis and inflammatory reaction were more recent and more intense than those seen in case L. M. These markedly necrotic lesions in the inner layers of the retina were infiltrated by polymorphonuclear leucocytes, lymphocytes, eosinophils and plasma cells, and similar cells mingled with fibroblasts and capillaries growing out into the vitreous. Dislocation of the degenerated retinal layers with extrusion of portions of the hypertrophied pigmented layer into the inner layers was seen in these lesions, as well as diffuse astrocytosis and capillary hyperplasia. The choroid showed varying degrees of infiltration, chiefly by lymphocytes and plasma cells, predominantly in the chorio-capillary layer and in regions adjacent to retinal lesions. The sclera was normal."

Hence in both eyes a focal chorioretinitis is present. Perivascular cell-infiltrations were found in one of the external ocular muscles. A number of parasites were also present.

The next histopathological observation is the subject of the publications of ZUELZER, HEATH and HEATH and ZUELZER.

One of the children of a prematurely born twin (case H.) died a month after birth of toxoplasmic encephalitis.

The authors make no mention of an examination of the eyes while the child was alive. They examined only one of the eyes histologically and with the following result :

"The size was smaller than is normal for a full term baby. The pupillary areas showed a persistent vascular blood-containing fetal membrane and partly inflammatory remnants, some of which were attached to the capsule of the lens, as seen in fetal iritis. The stroma of the iris was loose, edematous and negroid. Increased pigment was noted in the anterior portion of the stroma, due to migration from a deep layer. The two pigment layers of the retina were edematous. The ciliary body was loose edematous. The ciliary processes were well developed, were loose and open and showed dis-

sociation of pigment, plasma cell-infiltration and a few nucleated erythrocytes. On the surface of the processes were noted a few plasma cells and monocytes. The conjunctiva near the limbus showed a few small foci of perivascular lymphocytes. The extraocular muscles at their attachment to the globe showed a few thin foci of lymphocytes and plasma cells. The vitreous was coarsely fibrillar and contained a few cells mostly large mononuclears.

The choroid was well differentiated but more cellular than that of an adult. It showed extensive involvement, with rather sharply bordered destructive granulomatous lesions accompanying the retinal foci. Edema was severe and dissociation of structure, migration of pigment and extensive venous congestion (vessels contained nucleated red cells) were present; capillary hyperplasia and vascular proliferation were not significant. The retina was for the most part artefactitiously separated but showed areas of subretinal hemorrhage. The granular layers were well developed, and the outer showed few oval nuclei. Cones and rods were partly destroyed in areas associated with hemorrhage and appeared ill-formed (partly due to fixation and processing). The granular layers were not so compact as in the adult state. The ganglion-cell layer was poorly represented. The pigment layer of the retina was of a heavy negroid type. Müllers fibers were greatly exaggerated and hyperplastic in the inner layers, which were not fully differentiated and showed new connective tissue. The nerve fiber layer was loose, wide and disarranged. A few plasma cells, lymphocytes and mononuclear cells had infiltrated, and histiocytes, storing pigment and debris were noted. An occasional cystlike aggregate of toxoplasmas was seen in the inner nuclear layer, and not in the severe destructive granulomatous areas in the retina. One cluster was observed at the level of the nerve fiber layer. Inflammatory foci were mostly retinal and gave the impression that this layer was the point of origin. The macular area was occupied by a large, swollen necrotizing lesion. Plasma cells were noted in moderate abundance, as well as a few lymphocytes. The necrotizing retinal lesion showed disintegrating cells, some of which had been flung into the vitreous. Dissociation and migration of pigment were pronounced as one proceeded inward. Hemorrhage was noted on the surface of the retina. No parasites were seen in the necrotizing lesion.

The optic nerve in longitudinal section showed persistence of the hyaloid artery extending partly into the vitreous. Edema bordered the central vessel meniscus, and the nerve head was likewise edematous, no foci were noted in the optic nerve substance. The leptomeninges showed foci of lymphocytic infiltration. The impression was that the inflammatory process was unusually severe, selective and discrete and had not had time for repair. The pigment had not collected in depots, and no fixed scar had developed. No calcium was noted in the retina or the choroid."

The eyes showed diffuse acute iridocyclitis and a sharply localized destructive and inflammatory lesion of the retina and the choroid in the macular region. HEATH and ZUELZER mention that they had found toxoplasmas in the retina. In this case there was a persistency of fetal blood-vessels in the pupil, associated with inflammation (fetal iritis).

The other child also appeared to suffer from encephalomyelitis and chorioretinitis later on. The presence of toxoplasma neutralizing anti-bodies in the serum of this child and of the mother confirms the diagnosis of toxoplasmosis in this child, too.

BAMATTER (3) gave a detailed and beautifully illustrated microscopical description of ocular lesions. In this case, too, one of prematurely born twins died of a congenital toxoplasmic encephalitis.

There is a nystagmus and deviation of the eyes. The pupils are unequal and react but slowly to intense light. In the left fundus oculi a large grey lesion was observed in the macular region, surrounded by pigment.

The child died at the age of 27 days with increasing symptoms of encephalitis.

Both eyes showed inflammatory changes. BAMATTER thinks that infection of the eyes took place some weeks before birth. The differentiation of the tissues in both eyes was found to be normal.

On a postmortem examination it struck one that the eyes were small. Prior to death this microphthalmy had not been striking. The anterior eye-segment, the lens and the vitreous are normal and show no inflammatory changes. The choroid, the retina and the optic nerve show focal inflammatory lesions. There is a mild interstitial neuritis optica and perineuritis. In both eyes there is a fresh focal chorioretinitis principally in the posterior segment and in the macular region. The intensity of the inflammation in both eyes is different, as well as the age of the inflammatory process. In the retina there are large swollen hemorrhagic-necrotic zones with the formation of abundantly vascularized granulation-tissue changing into scar-tissue. The pigmented layer of the retina has entirely disappeared with migration of the pigment, especially at the edges of the necrotic zone. The structure of the retina has been lost entirely. The choroid is swollen, hyperemic, and infiltrated with lymphocytes and plasmocytes. In an apparently advanced stage of the inflammation there was a thin layer of scar-tissue, replacing the retina and lying on a hyperplastic choroid membrane. BAMATTER found toxoplasmas in both eyes, especially on the border of the necrotic tissue of the retina, both as pseudo-cysts and as isolated ones.

Typical hemorrhagic-necrotizing and productive changes in the retina and choroid, and inflammatory signs in the optic nerve are the main ocular lesions present.

KEAN and GROCOTT (2) also made microscopical examinations in a case of congenital toxoplasmosis. Unfortunately they were not able to examine the eyes during lifetime, since their patient was in a very bad state and died when only 10 hours old.

They do not state if both eyes or only one of them were examined. They described the changes found in a few lines:

"An intense granulomatous chorioretinitis was present. Parasites were few and could only be found after prolonged search, as small cystlike aggregates of three or four toxoplasmas. Although an inflammatory reaction was present, no parasites were seen in the optic nerve."

GASSER and SCHWARZ's case : [1])

Both eyes are badly "deformed". There is a pronounced microphthalmy (the cornea-diameter amounts on the right to 5 to 6 mm.) and enophthalmy on both sides. Mention is also made of a "cataracta congenita", the presence of synechiae posteriores and iris bombans.

The child succumbed at the age of 11 months. GASSER and SCHWARZ found a chronic chorioretinitis in both eyes and deposits of calcium in the vitreous and in the anterior lens capsule.

The eyes are small. The vitreous is greatly shrunken. Both sclera and cornea show microscopically no changes at all. The anterior lens capsule is structureless, considerably thickened, and shows accumulations of granular calcium material. Only on the anterior and posterior pole of the lens are there any remnants of the lensepithelium to be recognized. The principal substance of the lens is structureless. The retina shows very intense changes. The pigmented layer is to be recognized in places only.

The retina is thickened consisting of reticular elements and accumulations of cells showing a neuroma-like arrangement. Between them are groups of lymphocytes and plasma cells. At the internal border of the retina there are also calcium granules in varying numbers. The choroid has evidently grown thicker. In the zona vasculosa are well-defined lympho-plasmocytic infiltrations with isolated eosinophils. The ciliary body shows the same changes as the retina.

* * *

Toxoplasmas in the retina of a spontaneously infected fowl have been described by HEPDING.

The external symptoms of the eye were chemosis, epiphora, temporary cloudiness of the cornea and changes of form and colour at the pupillary border of the iris. The optic nerve was found to be brittle and yellow-coloured by necrosis. In the iris, ciliary body, vitreous and choroid there was considerable cellular infiltration. The retina is likewise heavily infiltrated and in the posterior pole of the eye principally around the optic nerve, is an extensive necrosis of all the layers of the retina. The nerve tissue is also wholly necrotic in the optic nerve and there is considerable infiltration of lymphocytes and an increase of fibro-blasts. In the ocular muscles and in the orbital tissue there are peri-vascular infiltrations.

Hence there was serious panophthalmy. In the retina there were numerous toxoplasmas in pretty well all the layers, the clearest being in the layers poor in nuclei, in the form of schizonts, clusters of tomonts and isolated tomonts. It struck HEPDING that a particular accumulation of cells around the toxoplasmas did not occur. HEPDING found toxoplasmas nowhere else than in the retina, although cell-infiltrations were found in the brain and in the plexus ischiadicus. Spontaneous toxoplasmic retinitis is unknown in other animals.

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[1]) BAMATTER in the meantime identified this case as toxoplasmosis.

II. OCULAR SIGNS ASSOCIATED WITH POSITIVE SERUM TEST FOR TOXOPLASMOSIS

1. ASSOCIATED WITH COMPLEMENT FIXING ANTI-BODIES

In a case of „fetal toxoplasmic encephalitis" described by LEVIN and MOORE a bilateral chorioretinitis was noted when to child was 5 months old. Even then the fundus lesions were quite inactive.

"The fundi showed pallor of the nasal portions of both optic discs and several large areas of old chorioretinitis. These were located in the lower portion of the right fundus and in the upper temporal and lower nasal portions of the left. They were all sharply outlined and showed yellowish-white patches with accumulations of pigment, chiefly at their margins, but also within the atrophic areas. The vitreous was clear, and there were no hemorrhages or areas of edema in the retina."

The presence of inflammatory lesions in the fundi oculi induced the authors to assume that a disseminated infection was the cause of the cerebral symptoms, which they had not been able to explain before, and also to entertain the possibility of toxoplasma-infection.

2. ASSOCIATED WITH TOXOPLASMA NEUTRALIZING ANTI-BODIES

References to ocular signs are more numerous which are associated with the presence of toxoplasma neutralizing anti-bodies in the blood. The application of the toxoplasma neutralization test was, after SABIN had pointed it out in 1941, stimulated especially in ophthalmology. In the great ophthalmological centres in North America, a relatively large number of cases of chorioretinitis, whether accompanied by other symptoms or not, were examined. So doing it was found that a not insignificant part of the patients examined showed a positive neutralization test, which led to the assumption of a toxoplasma-infection in these cases.

The ocular lesions are not always described in detail.

WOLF, COWEN and PAIGE (6) found a positive neutralization test in 6 patients from 8 months to 11 years, who in addition to other symptoms of infantile toxoplasmosis, had chorioretinitis. In 2 of the cases toxoplasmic infection was also confirmed in another way, namely by transmitting the toxoplasmic-infection to animals (case P. D. and case J. F.).

Together with the ophthalmologist KOCH, they gave a detailed description of the ophthalmoscopic picture and the course of the fundus-changes (KOCH, WOLF, COWEN and PAIGE).

When KOCH c.s. compared the chorioretinal lesions in these 6 cases, they came to the following summary of their observations :

"The earliest lesion was that seen in the macular area of the left eye of case 2. This acute lesion was characterized chiefly by localized edema, by indefinite demarcation, by early central necrosis that approximated the position of the fovea and by retention of the normal appearance of the retinal vasculature. A somewhat further developed lesion was seen in the macular area of the right eye of the same infant. This exhibited a lesser degree of edema, with a central chorioretinitis that was already moderately well advanced, particularly in the area corresponding to the fovea. In this central zone chorioretinal atrophy was sufficiently advanced to permit visualization of the underlying sclera. Pigment clumps appeared at the border of the central atrophic area and were more diffusely granular in and at the periphery of the less edematous marginal zone. Two smaller, tubercle-like additional foci of atrophy and pigmentation at the nasal periphery of the main lesion were possibly less advanced.

The large, convexly curved lesion in the upper temporal quadrant of the left eye in the same patient was definitely older than the two just described and might be considered an example of a subacute lesion. This was evidenced by sharp margination, lack of local edema and a band of irregular depressed old inactive pigmented chorioretinitis with atrophy at its borders. This protuberant area was singularly structureless and probably represented an avascular homogeneous fibrous mass which developed from granulation tissue that had invaded the vitreous.

A lesion in the upper nasal quadrant of the left eye in case 4 closely resembled the last lesion described and seemed to have reached the same stage of development except that numerous small marginal exudates of chronic edema were present in association with an ill defined band of bordering retinal edema suggesting a still active process or a recrudescence.

All the other chorioretinal lesions in the 6 cases as observed ophthalmoscopically were chronic and exhibited no activity. Essentially, they were sharply marginated areas of chorioretinal atrophy or proliferation of varying degree, with diffuse irregular pigment deposition, more concentrated at the margins. The retinal vasculature remained surprisingly normal.

The vitreous in all but 1 of the twelve eyes observed (the left eye in case 4) remained constantly clear, and the retina was entirely normal except for the portions immediately adjacent to lesions in the very active stages.

> Situation and number of lesions. — Multiple chorioretinal lesions, two to twelve in number, were observed in all the eyes examined except the left eye in case 2 and the left eye in case 1, each of which had only one lesion. In every instance there was a definite macular lesion, except for a small, doubtful area centrally in the left eye in case 4. The macular lesions were for the most part fairly large. The other lesions were either smaller satellite lesions or large areas in the relatively far periphery".

Besides the chorioretinitis there were other abnormalities : in 3 cases microphthalmy ; in 2 cases remnants of pupillary membrane ; lenticonus posterior, cataracta corticalis posterior and severe anisometropia each in one case, while refraction-anomalies were present in all cases. In some cases there was atrophy of the optic nerve head, which KOCH c.s. put down to various causes : papill-edema, destruction of the retina, intracranial processes and possibly inflammation of the optic nerve itself.

SABIN (4) found a positive neutralization test in ten patients with symptoms of infantile toxoplasmosis. They were children from 0 to 15 years of age. The children exhibited either cerebral calcification or chorioretinitis in the macular regions or both, in addition to various other manifestations. He fails to state the number of patients with chorioretinitis. Except stating that the chorioretinitis was in the macular region, SABIN gives no details about the ocular abnormalities.

VAIL, STRONG and STEPHENSON mentioned 6 patients from 7 to 23 years old with a positive neutralization test. In one of the cases the chorioretinitis had been acquired, in all other cases it was presumably congenital. The chorioretinitis was the only symptom and was mostly discovered at school age in connection with a poor vision. The chorioretinitis was both uni-lateral and bilateral, sometimes localized in the macular region and consisting of inactive or active lesions, which were occasionally sluggishly progressive. The lesions were sometimes slightly elevated, greyish-white in colour in the centre and bordered by dark pigment. Occasionally there was a choroidal hemorrhage round the lesion. It was usually in the direction of this hemorrhage that the lesion grew larger.

VAIL c.s. were of the opinion that toxoplasmic chorioretinitis is not typical, but that "many cases of chorioretinitis formerly diagnosed as tubercular, metastatic or of unknown etiology may be due to toxoplasma, especially if associated with cerebral calcifications".

CROTHERS mentions chorioretinitis and other symptoms of infantile

toxoplasmosis in 7 children up to the age of 12 with a positive neutralization test. In two families chorioretinitis was familial. CROTHERS does not describe the chorioretinitis in detail. Moreover toxoplasma neutralizing anti-bodies were found in the bloodserum of the mother and of two elder siblings of an infant suffering from hydrocephalia, microphthalmia and intracerebral calcifications.

In WAGENER's case with positive neutralization test, the child revealed an unilateral focal chorioretinal atrophy, not localized in the macular region.

HEATH and ZUELZER mentioned ocular abnormalities in a twin with infantile toxoplasmosis (case L. H.). Toxoplasmosis was diagnosed in this child on the presence of toxoplasma neutralizing anti-bodies in the serum and on the ground that the other twin had died one month after birth of a congenital toxoplasmosis, in which toxoplasmas were encountered in the brain and in the eyes. HEATH and ZUELZER describe the ocular abnormalities as follows:

"At 8 weeks the pupils reacted to light; vision was questionable; no fixation was noted; the corneas were hazy; threadlike extensions of the pupillary borders passed into the upper and lower quadrant. The discs were sharp, there were a few circumscribed lesions in the right macular area; the left pupil was undilated.

At 5 months one of us noted that the eyes were smaller than normal and showed irregular nystagmus and dissociation in movement, which was not limited. The left eye usually appeared to converge to about 30 degrees. The cornea of the right eye showed diffuse loss of normal transparency. The anterior chamber was shallow. The pupil reacted to light sluggishly. The patient was attracted toward bright light. The pupil dilated partially and unevenly under the influence of homatropine, owing to the partial persistence of the pupillary membrane and associate posterior synechia. Many vessels originated at the border of the pupil. The media showed some loss of transparency of the cornea, and the lens was apparently clear except where the anterior capsule was disturbed by the pull of the synechia. The vitreous showed diffuse haziness. The optic nerve head appeared congested and somewhat edematous, and the fine details were difficult to see.

Central vessels were noted on the nerve head. On the temperal side, including more than the macula and running over to the optic nerve, was a slightly elevated, whitish to ivory-coloured exudative retinal lesion. A similar, much smaller, lesion was noted in the mesial half of the retina about half-way between the nerve head and the periphery. The borders were round and showed areas resembling hemorrhage; the exudative process and the loss of transparency obscured the retinal vessels.

The left eye showed decided persistence of the fetal vessels around the entire circumference and a smaller, more irregular pupil (in spite of instillation of homatropine drops). It was even more difficult to make out the details in the left fundus, but a similar retinal lesion, resembling exudative chorioretinitis over a limited area, was noted in the temporal half.

Successive examinations of the fundi have shown that a slow recession of the retinal process is in progress."

"The characteristics of the early retinal changes, as illustrated in this case, were multiple bilateral large, whitish exudative, elevated macular lesions, which were fairly sharply bordered, sometimes with hemorrhage and were seen through an only moderately disturbed vitreous".

HEATH and ZUELZER make an interesting attempt to estimate the age of the fundus lesions described by them according to the presence or absence of the retinal vessels and their relation to the lesions. They conclude that the ocular lesions arose during the seventh month of fetal life.

SCHWARZ and WENDELL mention nystagmus, atrophy of the optic nerve head and chorioretinitis involving particularly the macular area, in two girls, five years of age.

HEIDELMAN found a positive neutralization test not only in presumably congenital chorioretinitis, but also in acquired chorioretinitis and uveitis anterior.

Altogether he examined 27 patients with congenital chorioretinitis and found in 17 of them (at ages varying from 1 month to 25 years) toxoplasma neutralizing anti-bodies in the serum. Among these 17 patients there were 5, who in addition to chorioretinitis manifested other symptoms of infantile toxoplasmosis.

Eight of 59 patients with acquired chorioretinitis and 4 of 38 patients with acquired uveitis anterior likewise had positive tests. These patients were 20 to 57 years old.

In the group of 27 patients with congenital chorioretinitis, the serum of whom HEIDELMAN examined, the chorioretinitis was bilateral in 25 cases ; in 48 of 52 eyes there was macular involvement, in 49 eyes the lesions were inactive and in 3 eyes active at the time of the examination. In 6 patients there was also microphthalmy present, while there was a high percentage of nystagmus and strabismus.

Of the 5 patients with congenital chorioretinitis and other symptoms of infantile toxoplasmosis showing a positive neutralization test, HEIDELMAN gives the following description :

"Case 1. Ophthalmoscopic examination showed that the media of the left eye were clear. In the macular region there was a large healed chorioretinal lesion, in the centre of which was a blue-green, egg-shaped elevation of the retina, with fibrous attachments extending into the vitreous. The disc was yellow-white. The remainder of the fundus was normal. The fundus of the right eye was obscured to the back of the lens. There was a macular lesion similar to that found in the left eye."

"Case 2 had microphthalmos, healed bilateral macular lesion and cerebral calcification at the age of 2 years. When he was re-examined at 7 years of age, the right pupil was almost occluded by adhesions of the iris to a cataractous lens, and vision was reduced

to the barest perception of light. Ophthalmoscopic examination of the left eye revealed a large, oval, inactive, sharply marginated chorioretinal lesion in the macula. The temporal portion of the disc was covered by a veil of glial tissue, which extended fanlike for a short distance and gradually blended with the normal retina on that side. The retinal arteries were moderately narrowed. The early description of the lesion in the right macula corresponded to that of the lesion in the left eye."

"Case 3. The chorioretinitis was of the disseminated circumscribed type."

"Case 4. In the left eye there was a chorioretinal lesion. An identical lesion had been described earlier in the right eye, but at the time of the examination the pupil on this side was occluded, as a result of later inflammation."

"Case 5. (L. H.) exhibited uveokeratitis at 1 month and cerebral calcification at 2½ months of age. The eyes were microphthalmic, but the fundi were not seen until the infant was 5 months old, when bilateral macular chorioretinitis was found."

Concerning the chorioretinitis, which should be regarded as acquired, HEIDELMAN says: "The ocular lesions in all patients were in the active stage at the time of the test, although some of the patients had a history or clinical evidence of previous inflammation in the same or in the other eye".

One of the cases, the mother of a child with congenital chorioretinitis was described as follows:

"She had a unilateral, round, non-pigmented, grayish-white, slightly elevated macular lesion, 1 disc diameter in size. On one occasion posterior corneal precipitates and an aqueous flare was noted in the same eye."

RUCKER makes mention of a "diffuse choroiditis of low grade" in a 51-year-old man with a positive neutralization test.

ADAMS described the ocular symptoms in a 14-month-old girl with toxoplasma neutralizing antibodies in the blood serum.

"A constant nystagmus and several bilateral areas of chorioretinitis with vitreous dust and floaters were present. The vitreous dust and floaters were considered to be possible signs of active infection. The chorioretinitis was first noted at the age of 6 months."

ADAMS c.s. found chorioretinitis in a 14-year-old girl (case C. G.). The serum neutralization test against toxoplasma was positive.

"Fundoscopic examination of the eyes showed a bilateral papilledema of about two diopters. The retina of the right eye had a large central area of degeneration with patches of black pigment, white exposed sclera, and some choroidal vessels. The area was about two disc diameters across and was sharply demarcated. The left retina had two smaller areas of degeneration which consisted of black pigment deposits one-fourth diameter across. These areas were interpreted as evidence of chronic chorioretinitis.

There was no indication that this was an active process. The visual fields for both eyes were normal peripherially, but there was a large central scotoma in the right field. The visual acuity was nearly zero in the right eye and 20/160 in the left."

JOHNSON c.s. are of opinion that the recognition of toxoplasmic "choroiditis" merely on the ground of the clinical picture is not very probable and that the serum must be examined "if a relatively certain diagnosis is to be made".

JOHNSON c.s. found toxoplasma neutralizing anti-bodies in 4 patients with congenital "choroiditis" at the ages from 3 to 5 years and in 16 patients with acquired "choroiditis" at the ages from 15 to 50 years.

This was the result of the examination of a group of selected patients with central lesions, active or inactive and a clear vitreous. The lesions were both unilateral and bilateral.

With one patient a quiescent chorioretinal lesion became active during each of three pregnancies :

"Mrs. Q. S., aged 22, had choroiditis early in the second month of her first pregnancy. After a mild febrile reaction to the injection of typhoid vaccine she miscarried. The choroiditis slowly subsided. A year later, when she was again gravid, the primary lesion in the left eye again became active, extending within a month to about twice the original size. There also appeared in the right eye a lesion about 2 disc diameters below the macula. This did not progress toward the macula, although no treatment was given. At term she was delivered of a normal baby. Post partum, the choroiditis in the right eye promptly became inactive and the larger lesion in the left eye gradually subsided. Nine months ago her third pregnancy was accompanied with moderately severe activity in the damaged (left) eye. Her request for a therapeutic abortion was granted as an aid in preserving the central vision in her right eye. After this third pregnancy there was no activity in the lesion in the right eye, and the lesion in the left eye became clinically inactive in the three months after the uterus was emptied."

JOHNSON c.s. see the explanation of the recurrent choroiditis in an activation of toxoplasmic pseudocysts during pregnancy, possibly chemohormonal.

Ophthalmologic examination in the case reported by MILLER revealed lateral nystagmus of both eyes, several large areas of chorioretinitis in the right eye and one large area of chorioretinitis in the lower quadrant of the left eye.

III. OCULAR SIGNS RESEMBLING THOSE SEEN IN TOXOPLASMOSIS

LICHSTEIN and SOLIS-COHEN described the following ocular abnormalities in a 22-year-old man with convulsions, mental retardation and cerebral calcifications.

"There was a horizontal and rotatory nystagmus present with movement to the right. Extensive choroidal changes were present involving both eyes, with a moderately advanced grade of optic atrophy. Large macular atrophic lesions were noted. Myopia of high grade was found. The lesions were believed by the ophthalmologist to be on the basis of a hereditary macular degenerative process, congenital and colobomatous in origin."

Whereas LICHSTEIN and SOLIS-COHEN mentioned this case as tuberous sclerosis, MERRITT and ARING, and KOCH pointed out that the atrophic nature of the fundus lesions and the absence of typical retinal tumors as seen in tuberous sclerosis, in combination with other symptoms rather suggest infantile toxoplasmosis.

KNAPP observed "a white mass with hemorrhagic areas and choroidal changes in the right eye and sub-retinal exudates and atrophic choroidal spots in the left eye", in a child that gave the impression of having been blind from birth. The ophthalmoscopic picture changed little if any in the course of a few years. KNAPP had toxoplasmosis in mind.

RICCI describes the lesions in a case which he considers to be toxoplasmosis, as "a quiescent, deep, chorioretinitic lesion 2 disc diameters in size, lying just nasal to the right disc and a similar lesion involving the macular area of the left eye. In the vitreous are membranous residues of exudates".

A detailed clinical description of the ocular signs in the case described by FREUDENBERG is given by BRÜCKNER [1]).

At the age of 3 weeks the fundus oculi was normal on both sides. Four weeks later the following abnormalities were noted : The pupils are on the instillation of homatropine only moderately dilated. In both eyes there is a ring of fibrin and pigment visible on the anterior lens-capsule corresponding to the size of the pupil in miosis. The iris is not hyperemic. The vitreous contains minute cloudy spots, more intense on the left than on the right. The fundus oculi shows enormous changes. Superiorally and on both sides of the papilla and also in the macular region are large, yellowish-white, ill-defined and slightly elevated lesions. These lesions are sometimes only separated by narrow zones of normal retina. At the border of the lesions there are small hemorrhages visible as is also the case in the lesions themselves. Two groups of lesions are to be distinguished namely : peripapillary and in the equator-zone. The lesions in the equator-zone are still larger and cover the greater part of the periphery of the fundus. In the periphery cumulation of pigment is seen at the border of the lesions.

The optic nerve heads are normal in colour. The retinal vessels are normal and transverse the lesions.

The condition of the eyes hardly change at all during the next few months. The pupils are only moderately dilated even under the influence of scopolamine. The precipitates on the lens disappear. The cloudy spots in the vitreous diminish somewhat.

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[1]) As has been stated toxoplasmas were found during the postmortem examination both in the brain and in the eyes.

The size and the colour of the lesions in the fundus do not change. Some of the peripheral lesions become somewhat sharper defined and the pigmentation slightly increases. The hemorrhages in the retina are resorbed.

Three days prior to the death of the child a presumably sub-retinal hemorrhage between the macula and the papilla arises. On both sides the optic nerve heads seem to be surrounded by granulations. There is no atrophy present nor edema of the optic discs.

Hence in both eyes there was an extensive and severe chorioretinitis and mild iridocyclitis. BRÜCKNER followed the development of the fundus lesions for some months.

RYERSON made mention of the following case :

A girl of seven perceived a dark spot before the left eye. An inactive macular lesion was found in this eye. When the girl was 19 she complained of spots before the right eye. There proved to be a large, active chorioretinitic lesion in the periphery of the fundus. There were cloudy patches in the vitreous and iridocyclitis. Activity of the fundus lesions varied in intensity.

On account of the commencement of signs in youth, the recurrent course, the iridocyclitis and the extensive chorioretinitic lesion, not described in detail, RYERSON entertained the possibility of toxoplasmosis.

GLANZMANN (1) describes 3 children with the remnants of a likely toxoplasmosis. In the first case there is a large, yellowish-white, sharply-defined and partially pigmented, old, inflammatory lesion in both maculae, reminescent of a coloboma of the macula, and bilateral atrophy of the optic nerve. In the second case, there is a bilateral microphthalmy, shallow anterior chamber and fixed pupils. It was not possible to evaluate the fundus oculi. In the third case there are a few small, old choroidal lesions, a shifting of pigment in the whole fundus and pallor of the optic nerve head.

CHAPTER V

TREATMENT

Experimentally the effect of various drugs on toxoplasma was studied both in vitro and in vivo.

A large number of anti-protozoal drugs belonging to the group of acridine-derivatives and to the antimony-, arsenic-, and the quinine-group were tested for their efficacy by SABIN and WARREN. Several compounds were found to be toxoplasmacidal in vitro, the strongest being atabrin and in a lesser degree trypaflavine, rivanol-lactate, potassium-antimony-tartrate, neo-salvarsan, tryparsamide, quinine hydrochloride, mapharsen and optochin (WARREN and SABIN), whereas parenteral and peroral administration of same (SABIN and WARREN) had no effect whatever on the course of infection in mice and rabbits. Diamidino-stilbene was found to have no effect neither in vitro nor in vivo (WARREN and SABIN) [1].

Several chemo-therapeutics were likewise tested by WARREN and SABIN for their efficacy. Sulfanilamide, sulfathiazole and sulfa-pyridine, in a concentration of 25 mgr. % had no toxoplasmacidal effect in vitro. Intra-muscular prontosil-injections as well as subcutaneous and intravenous injections with sulfa-pyridine were found to have no effect on infected mice and rabbits. A 1 % concentration of sulfa-thiazole and sulfapyridine in the diet did however have an effect on infected mice. The favourable action appeared to be dependant on a sufficiently high blood level. Mice, infected with small, but otherwise fatal doses of toxoplasma definitely recovered, while mice infected with larger doses survived so long as the chemo-therapeutics were given in the diet; when the administration was discontinued, the animals died after all. WARREN and SABIN accounted for this by assuming that the chemo-therapeutics check the multiplication of the parasites.

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[1]) In experiments carried on in the Institute for Preventive Medicine in Leyden, pentamidine proved to be effective in vitro, but not in vivo. These tests were made on rabbits. (Dr. WINSSER: personal communication).

The effectiveness of the sulfa-thiazole diet was only observed if the diet was begun not longer than 5 days after the infection. In the case of rabbits, too, a therapeutic effect of sulfa-thiazole was observed if a sufficiently high blood level was maintained by intra-abdominal injections.

Biocca and Pasquali confirmed the findings of Sabin and Warren. Biocca and Nobrega witnessed a therapeutic action against experimental toxoplasmosis after subcutaneous administration of sulfadiazine, dichlorone, 117 M and formilone in an oil suspension. These drugs appeared to be markedly superior to sulfathiazole (Biocca and Nobrega).

Weinman and Berne obtained better results than Sabin and Warren with higher blood levels of sulfonamides. By this it was possible to cure mice of a usually fatal infection, even if they began the treatment some considerable time after the infection, even a few days before the date of expected death. Tests with sulfadiazine and sulfathiazole were not sufficiently extensive to allow of conclusions being made, but sulfa-pyridine they found „strikingly successful" in curing acute toxoplasmosis in mice. They gave sulfa-pyridine suspended in cotton-seed oil injected subcutaneously or sodium-sulfa-pyridine in saline solution injected intra-peritoneally, 2 or 3 times daily during a period of 6 to 9 days. A longer administering had no effect. Blood-levels were obtained of 7 to 15 mgr. % and 10.5 to 25 mgr. % respectively. Whereas control mice died in about 15 days, Weinman and Berne witnessed a cure in pretty well all cases when treatment with sulfa-pyridine started 5 days after infection and in some cases even a few days before the date of expected death.

The experiences of Weinman and Berne are now more sanguine with a view to overcoming the acute stage of toxoplasma-infection in man than those of Sabin and Warren, who even a few days after infection observed no effect.

Weinman and Berne, however, found that the animals "cured" in this way were toxoplasma-carriers after all. Sulfonamides cannot be relied on to eradicate the carrier state (Weinman and Berne).

Penicillin-sodium was found to have no therapeutic effect in animal-tests (Augustine, Weinman and McAllister).

The action of drugs on patients has not yet been fully evaluated. In the few recoveries which have occurred there is no convincing evidence that this outcome was influenced by the medication employed.

The following drugs were tried: sulfanilamide (Pinkerton and

HENDERSON ; SABIN (2)), sulfadiazine and sulfamerazine (ZUELZER), sulfathiazole (WOLF, COWEN and PAIGE (6)), sulfathiazole and quinine (DAVEL c.s.), elkosine and antimony (FREUDENBERG). ADAMS speaks of the favourable action of acetarsone.

VAIL c.s. treated a patient with uveitis with sulfathiazole and typhoid vaccine, after which they noted that the uveitis became inactive. The inflammation recurred however, and sulfathiazole brought no improvement. The uveitis now became quiescent under the administration of sodium-iodide. Another patient was treated by VAIL c.s. with typhoid vaccine and later on with tuberculine injections without effect.

KRAUSE and SMITH studied the effect of a number of drugs in 32 cases of uveitis associated with positive serum tests. The evaluation of the result of the treatment was based upon subjective impressions, alterations of the visual acuity and of the visual field, and upon the presence of signs of activity of the inflammation (exudation, hemorrhages).

In several cases the uveitis was in a chronic stage or in a state of regression already before treatment started. Moreover the number of drugs tested in relation to the number of patients is rather high. All this rendered the evaluation of the results of the treatment in many cases difficult. Yet KRAUSE and SMITH think that the administration of sulfonamides (in doses of 4 to 7 gm. daily) during a period of fever-therapy (produced by 3 to 5 injections of typhoid vaccine varying from 15 to 130 million units and given over a period of 7 to 14 days) may have value. KRAUSE and SMITH used sulfadiazine, sulfa-pyridine and sulfathiazole. Sulfonamides alone seemed to have little or no effect on the disease. Atabrine apparently gave some subjective and objective improvement. Penicillin, vitamins, potassium-iodide, vasodilatators and many other drugs produced no demonstrable change in the course of the disease.

FREUDENBERG gave transfusions of blood-plasma of the mother hoping that this would contain neutralizing anti-bodies.

ADAMS mentions the favourable action of cauterizing a part of the choroid plexus as treatment of progressive hydrocephaly in toxoplasmosis.

PART II

OWN OBSERVATIONS

CHAPTER VI

DESCRIPTION OF CASES

I. TOXOPLASMIC RETINO-ENCEPHALOPATHY VERIFIED BY TRANSMISSION OF THE INFECTION TO ANIMALS AND BY HISTO-PATHOLOGIC EXAMINATION (CASES 1 AND 2)

The cases 1 and 2 are instances of fatal toxoplasmic-infection in infants. There is a striking similarity in the clinical picture and the course of the illness in both cases. The clinical picture is characterized by the symptoms of retino-encephalopathy. The children succumbed when they were $2\frac{1}{2}$ and 3 months old respectively.

CASE 1 [1]) : A. v. D., a boy, born 7th November 1947, was admitted into hospital when he was 10 days old on account of feeding-trouble and exsiccation.

FAMILY HISTORY : The first child was born prematurely after a pregnancy of $6\frac{1}{2}$ months and died soon after birth. The mother had diphtheria at the time. The second child is normal. The patient is the third child. The mother was never ill during the pregnancy. She has no abnormalities in the fundus oculi. The toxoplasma neutralization test with the serum of the mother is, both with respect to the Bk-strain and with respect to the SABIN-strain, positive. The toxoplasma neutralization test with the spinal fluid of the mother is negative with regard to the Bk-strain.

PERSONAL HISTORY : The child was born prematurely by one month. The birth went off normally, the child crying at once. It never fed properly.

PHYSICAL EXAMINATION AND COURSE : The weight is 2130 grammes. The body-temperature is 33.3° C. The child is normally built. The skin-turgor is fairly good. A mild form of jaundice is present. The heart and the lungs manifest no abnormalities. The circumferentia magna of the head amounts to 36 cm. The cranial-sutures are wide and the fontanel is somewhat taut. The veins of the head are clearly visible.

The child became dazed some days after its admittance into hospital. The fontanel is bulging now. It seems that the right arm moves less than the left. The child suddenly goes cyanotic with cold perspiration on its nose, irregular respiration and irregular action of the heart. Later CHEYNE-STOKES respiration sets in.

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[1]) This case is going to be published in full by Dr. ZIEDSES DES PLANTES.

Respiration continues to be irregular. The attacks of cyanosis persist. Now and then convulsions occur. The temperature varies considerably, being mostly sub-normal. The size of the head at first gradually increased, but later on decreases, the cranial-sutures disappear and the bones of the skull overlap, thus giving rise to scaphocephalism. Some blisters arise on the thumb and index-finger of the right hand and on the index-finger of the left. Therapeutically sulphathiazole and, later on, percoccide is administered (½ gm. daily). The child succumbed when 8 weeks old.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : A mild form of hydrocephalia is present. A few, not very intense shadows are visible, apparently caused by intra-cerebral calcium deposits.

LABORATORY DATA : Examination of the Ventricular Fluid : The ventricular fluid both from the right and the left ventricle has been examined several times. It is xanthochromic and cloudy on both sides, more on the left than on the right, and is under increased pressure. It coagulates spontaneously. NONNE-APELT's reaction is decidedly positive and the number of cells have increased. The bilirubin test is weakly positive. On the 22nd November 1947 the protein content on the right amounted to 24.03 ‰ (albumin 15.03 ‰, globulin 9 ‰), on the left to 34.82 ‰ (albumin 20.64 ‰, globulin 14.18 ‰). The goldsol-test is intensely pathological.

In smears of the ventricular fluid stained with hematoxylin-eosine and with MAY-GRÜNWALD-GIEMSA toxoplasmas were present on several occasions. Cultures of the cerebral fluid remained sterile.

Examination of the Blood : erythrocytes 3.490.000, leukocytes 5.200 : eosinophils 6 %, polymorphonuclear leukocytes 37 %, lymphocytes 57 %.

VENTRICULOGRAPHY (22ND NOVEMBER 1947) : There appears to be no communication between the right and left ventricle. The foramen Monroi appears to be occluded on both sides. Both ventricles are dilated, the right more than the left, and have moved roughly 1 cm. to the right. The air introduced causes a "honeycomb pattern" of the ventricles on the röntgenogram (Fig. 3).

TRANSMISSION OF THE INFECTION TO ANIMALS : Four mice are inoculated intracerebrally and 1 intraperitoneally with the ventricular fluid. Only 1 of the intracerebrally injected mice survived. All the other animals died after 8 to 9 days of toxoplasma-infection. The toxoplasma isolated in this way is kept alive by regular mouse-passages. Intraperitoneal inoculation of 2 mice with blood and intracerebral injection of 1 mouse with the exudate from one of the finger-blisters, were negative.

OPHTHALMOLOGIC EXAMINATION (12TH DECEMBER 1947) : The child reacts to light by blinking. Divergent strabismus is present. Both eyes lie deep in the orbit, and are very small. The horizontal measurement of the cornea amounts to 7½ mm. Both anterior chambers are opaque. The irises are hyperemic. The pupils react very little and sluggishly to intense light. On the instillation of atropine the pupils dilate but moderately and are not quite round. Adhesions of the pupillary border of the iris to the anterior capsule of the lens are visible (Fig. 4).

The details in both fundi are but indistinctly visible. In the right fundus there are no distinct abnormalities to be seen. In the left fundus, infero-temporally, a more or less triangular lighter zone is visible two to three disc diameters in size. This zone is not sharply defined and is slightly pigmented (Plate I).

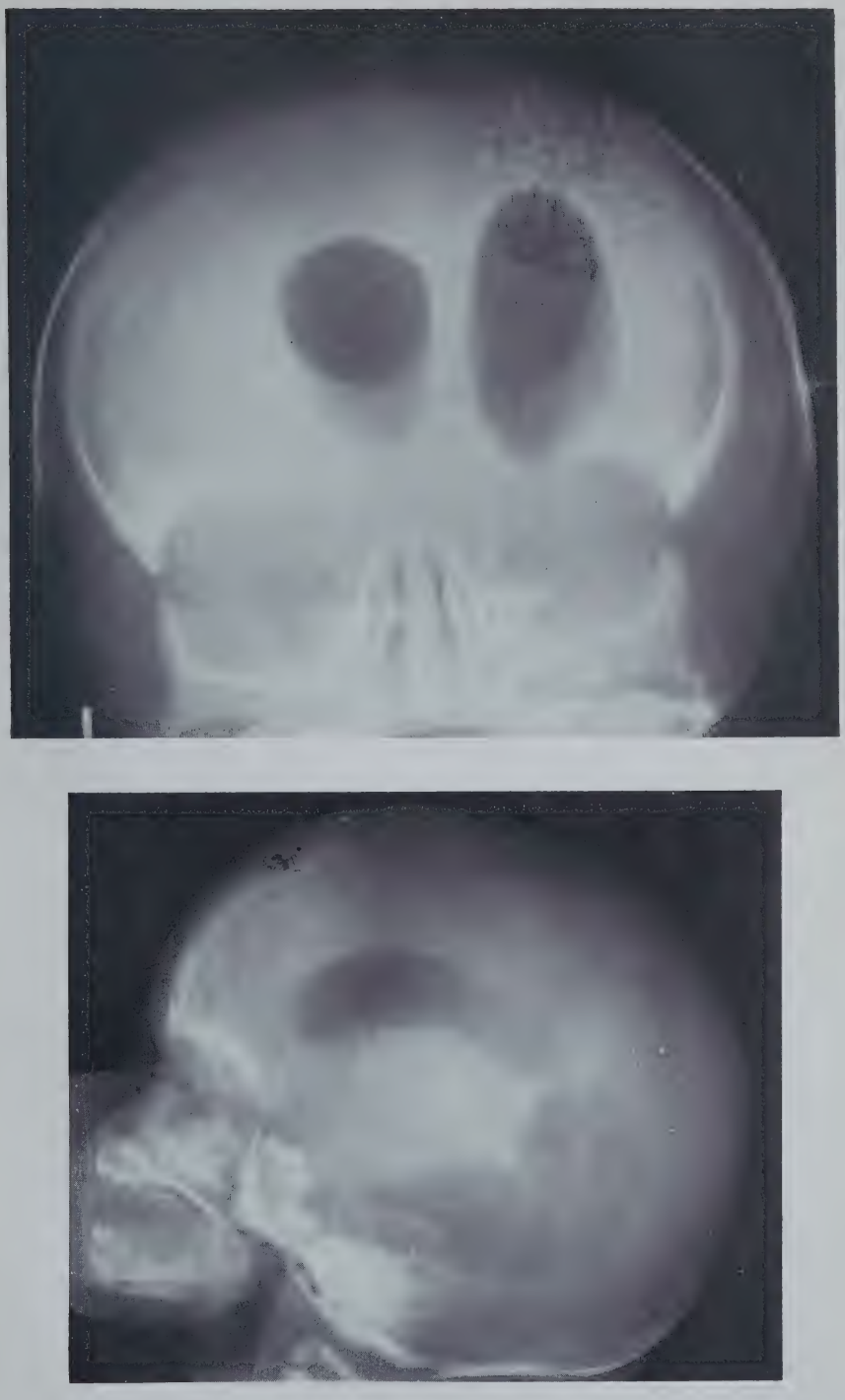
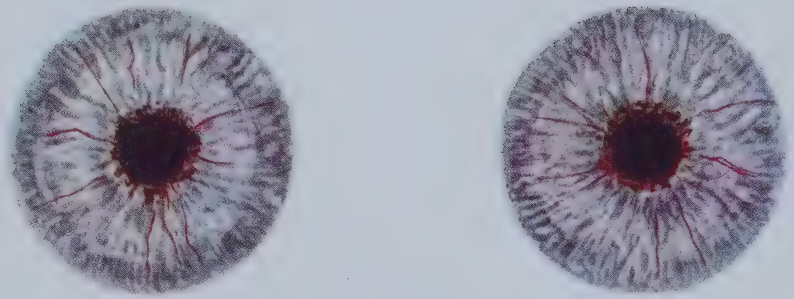


Fig. 3: Case 1. Hydrocephalia. Dilated and displaced ventricular system.
(Courtesy of Dr. B. G. Ziedses des Plantes)



Right eye Left eye

Fig. 4 : Case 1. Toxoplasmic iritis. Microphthalmia (horizontal diameter of the cornea $7\frac{1}{2}$ mm.).

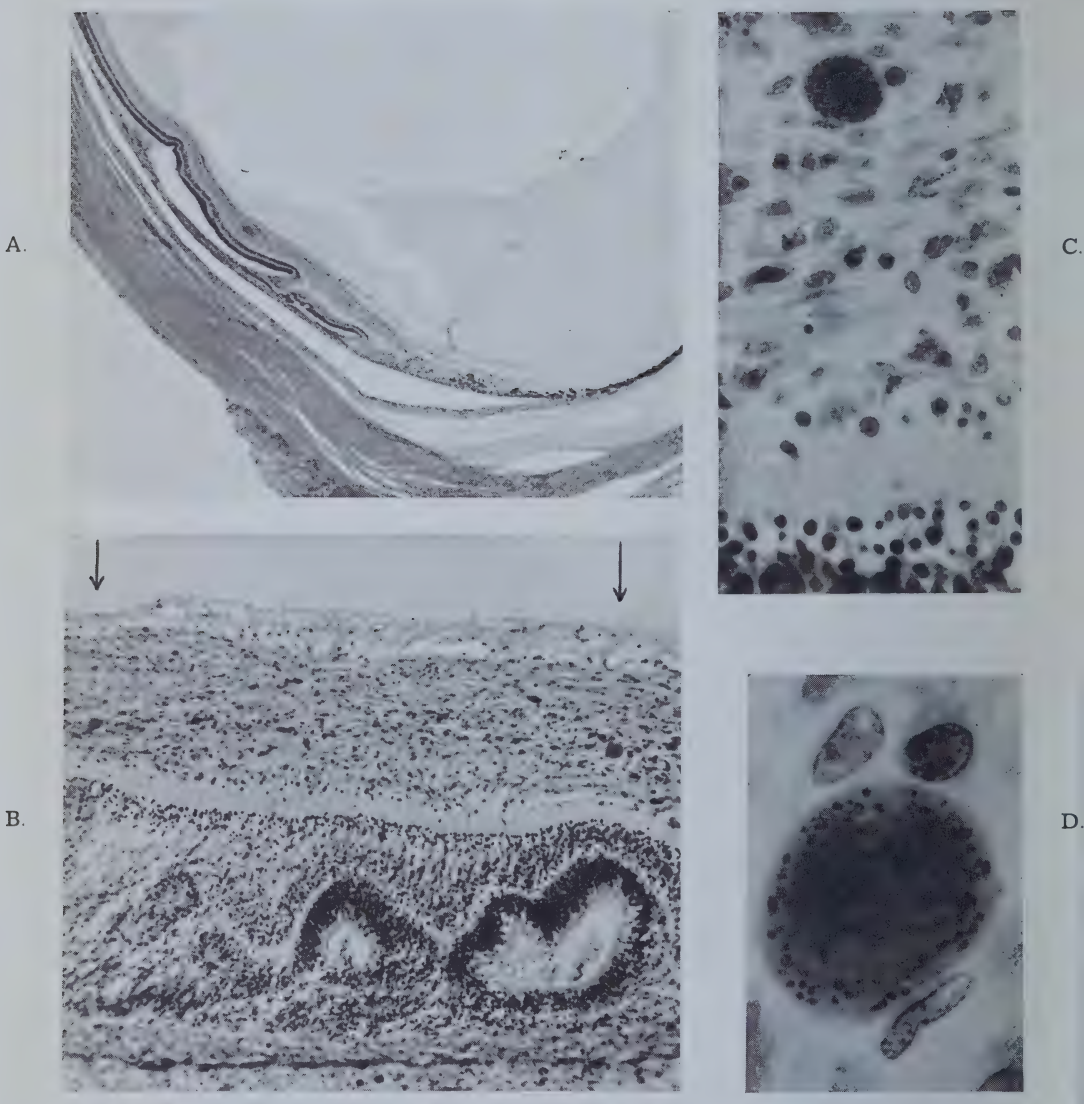


Fig. 5 : Case 1. Toxoplasmic retinopathy.
A, B : Chronic-proliferous retinal lesion with toxoplasma colonies (↓).
C, D : Toxoplasma colonies.

Hence the child shows divergent strabismus, bilateral enophthalmy and microphthalmy. There is iritis present in both eyes. In the left fundus oculi there is a focal, slightly pigmented lesion to be observed.

MICROSCOPIC EXAMINATION OF THE EYES : (Fig. 5)

Right eye : The cornea, sclera and external muscles of the eye show no abnormalities. Against Descemet's membrane and on the anterior lens capsule there are some isolated pigment- and cell-clumps. The blood-vessels of the iris and the ciliary body are all dilated. There is no cellular infiltration in the iris and ciliary body. In a few places there are adhesions of the iris to the anterior capsule of the lens. There are remnants of a membrana pupillaris persistens. Between the processus ciliares and in the vitreous there are a few cells.

The pars plana of the ciliary body and a part of the choroid have separated from the underlying sclera, connected with it by thin tissue septa. The structure of the lens is normal. The choroid is greatly thickened having roughly three times its normal thickness. The choroidal vessels are considerably extended. Here and there in the choroid there are a few lymphocytic infiltrations. The pigmented epithelium and the retina are affected over an area extending from the ora serrata backwards. At the ora serrata the retinal structure has entirely disappeared, the retina being substituted by a loose young granulation tissue. This granulation tissue has overgrown the considerably folded remnants of the retina and continues as a thin layer of connective tissue into the nerve fiber layer of the retina to far beyond the equator. The pigmented epithelium is partially destroyed and has partially proliferated. There is slight infiltration of the retina with lymphocytes and plasmacells.

In the retinal lesion there are various round forms about 25 μ in size and consisting of colonies of a large number of toxoplasmas. Isolated toxoplasmas are nowhere encountered.

In the optic nerve there is an increase in the connective tissue. The optic nerve head protrudes some distance into the vitreous.

Left eye : On the whole the changes in the left eye are the same as those in the right. The chronic-proliferous retinal lesion reaches from the ora serrata still farther in the direction of the posterior pole of the eye than in the right eye. Toxoplasmas were not observed in the left eye.

Hence in both eyes there is a chronic-proliferous focal retinitis in which, in the right eye, toxoplasma colonies are met with. There is a probably toxic irritation of the uvea and an incipient atrophy of the bulb together with atrophy of the optic nerve.

SUMMARY : Internal hydrocephaly is found to be present in a boy prematurely born by one month, a few weeks after birth. Probable streaks of calcification are visible on the X-ray photograph of the skull. There are various disorders of a cerebral nature : daziness, a considerable lability of the body-temperature, irregular respiration, attacks of cyanosis and convulsions. The ventricular fluid is xanthochromic and cloudy, containing an increased number of cells and a considerably raised percentage of protein (as much as 34.82 $^0/_{00}$). The gold-soltest is intensely pathologic. There is slight eosinophilia in the blood. In smears of the ventricular fluid organisms resembling toxoplasmas

were encountered. Toxoplasma-infection was transmitted to animals and a strain of toxoplasma was isolated in this way. The child succumbed at the age of 8 weeks.

The toxoplasma neutralization test with the serum of the mother is positive, both with respect to the Bk.-strain and to the SABIN-strain of toxoplasma; the neutralization test with the spinal fluid of the mother is negative with regard to the Bk.-strain.

At the age of 5 weeks, the following ocular symptoms were observed: divergent strabismus, bilateral enophthalmus and microphthalmus, iritis in both eyes, and a focal lesion in the left fundus. On a histological examination of the eyes, a chronic-proliferative retinitis was found to be present. In the retinal lesion in the right eye toxoplasma-colonies were encountered.

Hence the child manifests a syndrome of toxoplasmic retino-encephalopathy.

CASE 2 [1]): A. BK., a boy, born 15th June 1947, was hospitalized at the age of 6 weeks because of convulsive seizures, fever and enlargement of the head.

FAMILY HISTORY: The parents of the child had always been healthy. A röntgenological examination of the thorax and skull of the mother yielded nothing particular; an ophthalmoscopic examination proved both fundi oculi to be normal. The mother has a 1½-year-old normal son.

Toxoplasma neutralization tests with the serum of the mother gave positive results, both with respect to the Bk.-strain and to the Sabin-strain.

PERSONAL HISTORY: It is a second child. The delivery had a normal course. During the first few weeks of the child's life, the parents noticed nothing in particular about it. At the age of 4 weeks, it showed muscle twitching, rigidity of the muscles and opisthotonos. It had a temperature. The child went off its food. The head rapidly increased in size.

PHYSICAL EXAMINATION: There is a pronounced hydrocephalus with wide cranial-sutures. The eyes look downward. There is a spasticity of the neck and of the legs. The reflexes are lively and there is a positive sign of Babinski. It hurts the child to be touched. The head is held back. Shortly after being admitted into hospital, convulsions set in, which discontinued on luminal-sodium being administered.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL: There are dubious small specks visible in the brain suggesting calcium-deposits.

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[1]) This case has been published by DAVEL, VAN DER ELST, WINSSER, VAN THIEL and VERLINDE. With the exception of the clinical and histopathological description of the eyes, all data have been taken from DAVEL c.s. See also WINSSER c.s.

VENTRICULOGRAPHY : The left ventricle appears to be moderately dilated and moved to the left. The right ventricle is likewise moved to the left to beyond the median plane. An attempt to get air from one of the ventricles into the other was not successful. No fluid could be obtained by cisternal and lumbar puncture. Hence both foramina Monroi appeared to be obstructed. By introducing air into the ventricles a "honey-comb pattern" became visible, which may be explained by the very high protein content.

LABORATORY DATA : Cerebrospinal fluid : Ventricular punctures were made on several occasions. The cerebrospinal fluid was invariably xanthochromic. The protein content has been considerably increased (to 2.4 %). The cell content varies. The tryptophan test is positive. The gold-sol test is pathologic.

In smears of the cerebro-spinal fluid stained with methylene blue, in addition to mononuclear cells, crescent-shaped organisms were found, roughly 6 to 7 μ in length and 2 to 3 μ in width, with tapering ends and with a nucleus at the blunt end. This discovery, together with the clinical picture, aroused the suspicion of toxoplasmosis being present. The parasites were continually being met with in the ventricular fluid, but later on less numerous than at first.

Blood : There is a slight leucocytosis with an increased number of lymphocytes and of eosinophils (5 %).

No parasites were found in the blood, nor in the urine, nor in the bone marrow.

TRANSMISSION OF THE INFECTION TO ANIMALS : A strain of toxoplasma was isolated by intracerebral inoculation of mice with ventricular fluid. Of 10 inoculated mice 8 of them died from toxoplasmosis. Guinea-pigs failed to react to intracerebral injections of ventricular fluid. The isolated toxoplasma-strain was found to be immunologically identical or very closely related to a toxoplasma-strain, furnished by SABIN.

COURSE : Convulsions occurred once more during the further course. A fortnight after admittance to hospital, the temperature became normal. As a consequence of repeated ventricular punctures, the size of the head did not greatly increase. The child vomited much and its general condition rapidly declined. The child died when 13 weeks old. Therapeutically sulfathiazole and quinine were given.

OPHTHALMOLOGIC EXAMINATION : We examined the eyes at the age of 9 weeks and again at 12 weeks. The child fails to react to objects and to light. The eyes are almost constantly making conjugate movements to all sides. There is mild convergent strabismus. The bulbs are of normal size. Both corneae are clear and measure horizontally 10.5 mm. The pupils react to light, are round and are of the same size. On the instillation of homatropine, they dilate normally ; there appear to be no synechiae. The lenses are clear on both sides, the vitreous likewise. The fundi are clearly visible.

Right fundus oculi : The papilla n. optici is greyish-white in colour and is sharply defined. The fundus colour is greyish-brown in the periphery. The blood-vessels of the retina are slightly twisted here and darker coloured. The picture suggests a detachment of the retina.

Left fundus oculi : This shows exactly the same picture, but moreover there are infero-nasally in the extreme periphery several small yellowish-white spots visible surrounded by a darker zone.

The above-described picture became evident at the age of 9 weeks and appeared to have altered little a week prior to death.

AUTOPSY : Gross observations : There is an internal hydrocephalus and a stenosis of the aqueduct of Sylvius. Both foramina Monroi are wide open in contradistinction to the ventriculographically drawn conclusion. In the white substance of the brain are a few cavities of roughly 1 cm. in diameter. In the wall of the ventricles there are some yellow lesions to be seen.

Microscopic Observations : In the leptomeninges and in the ventricular wall there are mononuclear infiltrations. Mononuclear infiltrations were likewise seen perivascularly. In the ventricular wall there are some necrotic lesions surrounded by connective-tissue and granular calcium-deposits. Toxoplasmas are present in several inflammatory lesions. In the subcutaneous tissue, the musculus psoas and the diaphragma toxoplasmas are found, too.

MICROSCOPIC EXAMINATION OF THE EYES : Thirty-six hours after death, both bulbs were removed. Both eyes show the same histological picture. The external muscles of the eye, the cornea and the sclera exhibit no abnormalities. On the posterior surface of the cornea are some pigment- and cell-clumps. In the irisbasis there are some lymphocytes. In the ciliary body, too, there are a few lymphocytes. The choroid reveals no abnormalities. In the retina there are some folds of various sizes, a large retinal fold being found near the ora serrata. There is a small quantity of subretinal exudate under the folds. In one single place there is an inflammatory lesion around a blood-vessel in the retina consisting of lymphocytes, a few plasma-cells and a proliferation of the adventitia (perivasculitis retinae) (Fig. 6). On the optic nervi head is an obliterated blood-vessel. The nervous tissue of the optic nerve has disappeared almost completely and has been replaced by connective tissue (atrophia n. optici). The optic nerve-sheaths are infiltrated with lymphocytes and leukocytes (perineuritis optica).

SUMMARY : A boy born normally and who first showed no symptoms, fell ill at the age of 4 weeks with fever and convulsions. The size of the head increased rapidly. There were spasticity of the muscles, abnormal reflexes and opisthotonos. In ventriculography both ventricles appeared to have moved laterally and the right ventricle to be dilated. The ventricular fluid is xanthochromic and shows a marked increase in protein, a varying degree of pleocytosis, positive tryptophan test and pathological gold-sol test. In smears of the cerebro-spinal fluid many parasites resembling toxoplasma were encountered. By intracerebral inoculation of mice a toxoplasma-strain was isolated. The child manifested nystagmoid movements of the eyes and convergent strabismus. Ophthalmoscopically there appeared to be bilateral atrophy of the papilla nervi optici. The fundus-periphery is dark greyish-brown on both sides and the blood-vessels are tortuous giving the impression of a retinal detachment. In the extreme periphery of the left fundus there are a few small specks visible.

The child died at the age of 13 weeks. On a post-mortem examination being held, internal hydrocephalus and a chronic-necrotizing encephalitis were observed with toxoplasmas in several inflammatory

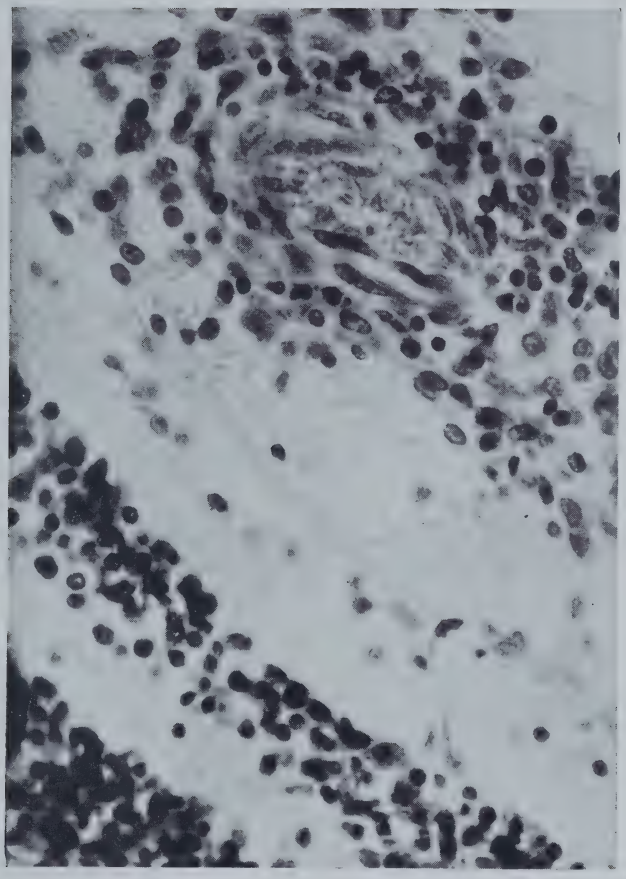

Fig. 6 : Case 2. Toxoplasmic retinopathy.
(initial lesion)

lesions. In the subcutis, the diaphragma and the musculus psoas, too, there were cellular infiltrations with toxoplasmas.

Microscopic Examination of the Eyes : There is a mild irritation of the iris and the ciliary body. At one single place perivasculitis in the retina is met with. The retina manifested several folds of various sizes. There is a mild perineuritis optica and a marked atrophia nervi optici.

No abnormalities were encountered in the other organs.

Toxoplasma neutralization tests with the serum of the mother gave a positive result both with respect to the Bk.-strain and to the SABIN-strain of toxoplasma.

II. RETINOPATHY AND RETINO-ENCEPHALOPATHY ASSOCIATED WITH POSITIVE SERUM NEUTRALIZATION TEST FOR TOXOPLASMOSIS (CASES 3 TO 13 INCLUSIVE)

The cases 3 to 13 inclusive are all characterized by retinopathy, either in an active stage or healed, in one or in both eyes.

The ages vary from 14 months to 54 years.

In the cases 3 to 9 inclusive, there are, in addition to the retinopathy, cerebral symptoms of a varying nature and intensity (retino-encephalopathy). In the cases 10 to 13 inclusive the retinopathy is the only demonstrable manifestation.

CASE 3 [1]) : E. W., a 4-year-old girl born 29th August 1939 was treated for convergent strabismus of the right eye.

FAMILY HISTORY : The father was always in good health. Except for some members of the family who suffer from diabetes mellitus, there has been no disease in the family of the father.

The mother has never been ill and invariably felt well during pregnancy. The patient was her first child. She has never had a miscarriage. After the birth of the child, she complains of headaches. A physical and an ophthalmologic examination failed to manifest any abnormalities. On an X-ray examination of the skull, 5 years after the birth of the patient, however, there appeared to be a pronounced thickening of the tabula interna of the bones of the skull resembling the type described as hyperostosis frontalis interna. She has given birth to 4 other children, all of which are healthy.

Toxoplasma Neutralization Test : The serum of the mother was examined on various occasions with respect to the Bk.-strain of toxoplasma. The rabbit-skin test was once positive and once doubtful.

PERSONAL HISTORY : The child was a full-term one and was born normally. The first months of its life the child gave no trouble at all. It has never shown any convulsions.

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[1]) BINKHORST (1, 2, 3).

Grasping at objects, lifting the head and sitting up were functions that developed rather late. The child learned to stand at the age of 12 months and walked when it was 18 months old. That the child slabbered much was very noticable at an early age. In the course of time this gradually increased. Vaccination took place at the age of 10 months, to which the child reacted by being pretty ill for a few days. Symptoms of encephalitis, however, did not manifest themselves. After the first year convergent strabismus began to make its appearance. Soon it appeared that mental development had been disturbed. It was not until the fourth year that the child made any efforts to speak. A physical examination when the child was three years old, disclosed an enlargement of the spleen. The child often stumbles in walking.

PHYSICAL EXAMINATION : The child is slightly built. The muscles are but moderately developed. It is always slabbering. It has a severe impediment in its speech ; it rarely ever makes any attempts to speak, in which case unarticulated utterances are made. The hearing is good. Its intelligence is defective. There is slight microcephaly. An examination of the internal organs and a laboratory examination of the blood and spinal fluid bring no abnormalities to light now. PIRQUET's reaction is negative more than once.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : Both bitemporally and fronto-occipitally several larger and smaller shadows manifest themselves in the brain, the shadows having the density of calcium shadows. They show a tendency towards symmetrical occurrence (Fig. 7).

OPHTHALMOLOGICAL EXAMINATION : The child gives the impression of being able to see fairly well. The fixation of objects is effected by the left eye. Right eye : There is convergent strabismus of the right eye. The right bulb is somewhat smaller than the left ; the horizontal measurement of the cornea amounts to 10 mm. right and 11 mm. left. The media are clear. There is a mixed astigmatism of approx. 4 diopters. Ophthalmoscopically there appears to be an almost round, focal chorioretinal atrophy of approx. 2 disc diameters in the macular area. An isolated choroidal blood-vessel is visible in the lesion.

The retinal pigment has partially been destroyed, while there is an accumulation of pigment especially on the border of the lesion. The lesion lies on the level of the fundus oculi. The temporal sector of the optic nerve head is pale (Plate II).

Left eye : The horizontal measurement of the cornea amounts to 11 mm. The media are clear. There is a simple hypermetropic astigmatism of approx. 1 diopter. On the first examination, the left fundus oculi was normal.

COURSE : The ophthalmoscopic picture of the right eye, which was first observed at the age of 4 years, has remained unchanged ever since. In the left eye, which did not show a single fundus abnormality on being first examined, there appeared to be a macular lesion 1 year later, consisting of a slight shifting of the pigment. In the infero-nasal sector, too, there was a small atrophic lesion with central pigmentation. During a further observation period seven small, round, grey foci in the retina were seen (Plate II). These foci disappeared in the course of a few months leaving no scar behind.

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. Animal Inoculation : When the child was 5 years old, an attempt was made to isolate toxoplasmas from the spinal fluid. Two guinea-pigs were inoculated intracerebrally for this purpose with the sediment. Both guinea-pigs were killed after 6 weeks.

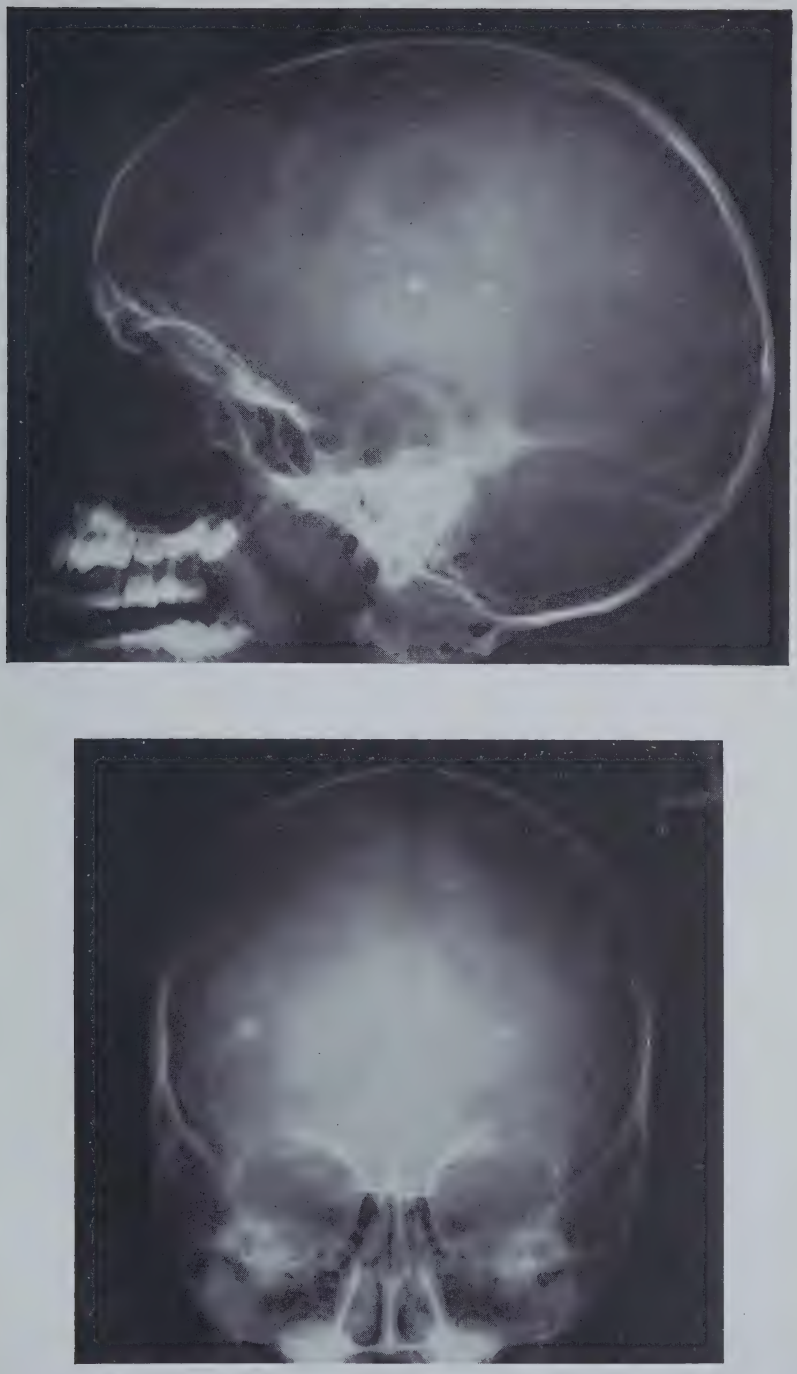

Fig. 7 : Case 3. Cerebral calcification.

In one of the guinea-pigs there was a local meningitis, in which no parasites were revealed. Serial passage of the brain likewise yielded a negative result in two subsequent guinea-pig passages and one mice passage. In the other guinea-pig at the place of injection there was a granulomatous lesion in the brain, in which a few cystlike aggregates of parasites resembling toxoplasmas were found. Another guinea-pig was inoculated with this brain-tissue. This guinea-pig was killed six weeks later and the brain was again found to contain a few parasites resembling toxoplasma. The parasites lay in the cerebral cortex without any cellular reaction. All ensuing brain-passages in guinea-pigs, rabbits, and mice were negative. Spontaneous parasitic infection was never observed in the experimental animals used.

B. Toxoplasma Neutralization Test: Two rabbit-skin tests made, turned out to be positive on both occasions. The Bk.-strain of toxoplasma was used in these experiments.

SUMMARY: A girl born normally and at full-term revealed, as the only symptom, an increasing slabbering during the first year of her life. The child appeared to be mentally retarded. She did not try to speak until she was 4 years old. Speech is still very defective, even now. A physical examination revealed an enlargement of the spleen when the child was 3 years old.

Afterwards physical and laboratory examinations were totally negative, with the exception of a general motoric weakness and a slight microcephaly. PIRQUET's reaction was negative. A röntgenographic examination of the skull at the age of five years revealed a number of areas of calcification in the brain. Convergent strabismus of the right eye developed after the child was 1 year old. A healed central lesion in the right eye was discovered at the age of four years. Fresh lesions appeared in the left macular area at the age of 5 years. There is microphthalmos on the right side. Toxoplasma-like parasites were encountered on the site of inoculation in the brain of one of two guinea-pigs intracerebrally injected with the spinal fluid and in the brain of one of two guinea-pigs of the second passage.

The toxoplasma neutralization test with respect to the Bk.-strain of toxoplasma was positive with the serum from both the patient and the mother. A röntgenographic examination of the skull of the mother revealed a thickening of the internal tabula of the bones of the skull.

CASE 4: C. v. D. L., a boy born 10th Nov. 1945, was brought to the ophthalmologist at the age of 11 months for convergent squint. Healed chorioretinal lesions were discovered. At the age of 2 years, the child was hospitalized for thorough examination.

FAMILY HISTORY: There are 3 children in the family. The patient is the youngest. The two other children have normal eyes. The eldest was born in 1930, was nursed

in a sanatorium in 1937 and in 1939, but is now healthy again. In 1931 the father underwent a rest-cure for an affection of the lungs and was cured later. He is a factory-hand.

Prior to her marriage the mother frequently had lymphomatous swellings in the throat and armpit. She felt ill during each period of pregnancy ; the last being the worst. She often had a temperature (up to 38.5 and 39° C.) and was often confined to bed. During the first 2 or 3 months of pregnancy she had a rash for a few days. She has never had a miscarriage.

The grandmother on the mother's side had 3 children after which she had 6 miscarriages in succession and finally 2 full-term still-born children. The last child that was still-born showed hydrocephaly. The two brothers and the sister of the mother are all healthy. A child of the sister of the mother is backward ; röntgenography of the skull and ophthalmoscopy are normal. A child of one of the brothers of the mother has alopecia areata ; the fundi oculi are normal. A niece of the mother is a deafmute.

The family have never kept any domestic animals ; but there was a very bad plague of mice.

The syphilis tests with the mother's blood are negative.

The toxoplasma neutralization test with the serum of the mother is negative with respect to the Bk.-strain of toxoplasma.

PERSONAL HISTORY : The child was born prematurely by a month. Delivery took place normally the child crying at once. It slept very much during the first month. After this its poor vision soon became evident ; it was always looking at its hands and never followed its mother about with its eyes. At the age of 3 months it had an abscess in the throat, which repeated itself at the age of 2 years. On both occasions the abscess was opened and drained after which it healed.

At the age of 6 months, the child had a severe convulsion that lasted about 10 minutes. Such-like attacks were never repeated. From that moment onward, the mother remarked that the child squinted. At the age of 1 year it was seen that the left eye lay deeper than the right.

The child's growth had always been poor and it was later in sitting up and walking than the two other children. At the first ophthalmological examination at the age of 11 months, besides a convergent strabismus, an already healed chorioretinitis was found. There was no further change in the fundus.

OPHTHALMOLOGIC EXAMINATION : The child recognizes its environment well and does not run up against anything. It can, however, only recognize large objects. He holds everything closer to him than a normal child does and looks at everything with the left eye.

The left palpebral fissure is narrower than the right. The left eye lies somewhat deeper in the orbit and is appreciably smaller than the right eye. The horizontal cornea diameter measures right 12 mm., left only 10 mm. There is convergent strabismus of the right eye. The movements of the eyes are normal.

Both pupils react to light. On the instillation of homatropine they dilate normally. The media are clear. The left eye has a myopia of 4 diopters.

Lesions are present in both fundi.

Right fundus oculi : In the macular region there is an oval, somewhat elevated lesion measuring from two to three disc diameters in size. The colour is grey-brown and at the border there is some dark pigmentation. The lesion is surrounded by a zone of depigmentation and atrophy of the choroid. Between the lesion and the papilla there

is a small focal atrophy and irregular pigmentation. Under the papilla there is a second localized, very dark-pigmented lesion of about the same size and somewhat elevated, likewise surrounded by a zone of depigmentation and atrophy. The papilla nervi optici is pale, the temporal sector is even considerably atrophic (Plate II).

Left fundus oculi : Under the papilla there is a globular, elevated grey-brown lesion bordered by a zone of dark pigmentation and measuring 2 disc diameters. Especially on the papilla side, it is surrounded by a flat atrophic zone. The papilla nervi optici is pale (Plate II).

RÖNTGENOLOGIC EXAMINATION OF THE SKULL : Bitemporally there is one and fronto-occipitally there are 2 minute calcium shadows to be seen in the brain-substance.

PHYSICAL EXAMINATION : The circumference of the head amounts to 49 cm. (the average for this age being 48 cm.). Heart, lungs, liver and spleen show no abnormalities. The reflexes are normal. The child takes small steps and its walk is uncertain, but there are no decided neurological disorders. PIRQUET's reaction and the MANTOUX test are negative.

LABORATORY DATA : There are no abnormalities in the urine nor in the faeces.

Examination of the Blood : The content of hemoglobine is 12 gr.%. Erythrocytes 4.410.000. Leukocytes 8.800 : eosinophils 4 %, basophils 3 %, polymorphonuclear leukocytes 51 %, monocytes 6 %, lymphocytes 36 %. The sedimentation rate amounts to 7/20. The syphilis tests are negative.

Examination of the Spinal Fluid : The spinal fluid is clear and colourless. The number of cells continues to be somewhat high (15 to 37/3) preponderantly lymphocytes. The percentage of protein is low (15—11 mg.%). NONNE-APELT's reaction is negative. The sugar content is approx. 60 % of the blood-level. The sodium chloride content is normal. The benzoin and gold-sol test are normal. The WASSERMANN test is negative ; the MEINICKE test is weakly positive. On a microscopical examination no micro-organisms were found.

MENTAL DEVELOPMENT : The child is of a cheerful disposition and is extravert. He speaks a few indistinct words. He is, however, intellectually backward. For quite long periods at a stretch, he makes, among other things, senseless movements with his whole body.

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. Animal Inoculation : 1st passage : five mice are intracerebrally inoculated with cerebrospinal fluid. 4 days later 2 of the mice are ill and are killed. Histological examination negative. 2nd passage : 5 mice are inoculated intracerebrally and intraperitoneally with a brain-emulsion from the animals out of the 1st passage. Six days later 1 mouse dies. 3rd passage : Five mice are inoculated intracerebrally with brain-emulsion. This passage is negative. Some months later the inoculation experiments are repeated in the same way with the same negative results.
B. The toxoplasma neutralization test with the serum is positive with respect to the Bk.-strain of toxoplasma.

SUMMARY : At the age of 6 months, a one-month-prematurely born boy has a bad fit of convulsions. After this, convergent strabismus persists, for which at the age of 11 months an ophthalmologist is consulted.

Quite early it was noticed that the child had bad vision. There is a left-sided microphthalmia and myopic refraction and on the right side convergent strabismus. Both optic nerve heads are pale ; the temporal sector of the right optic nerve head is even considerably atrophic. In the right fundus there are two and in the left fundus one quiescent, organized and darkly pigmented, inflammatory lesions, which, mainly on the papilla side, are surrounded by an atrophic zone.

Röntgenographic examination of the skull revealed two small shadows, possibly calcifications in the brain. Except for a slight eosinophilia in the blood, a slight pleocytosis and weakly positive Meinicke reaction in the spinal fluid, physical and laboratory examinations revealed nothing abnormal. There is a slight mental retardation. The child has had abscesses in the throat on two occasions.

The neutralization test for toxoplasmosis with the serum of the child is positive with respect to the Bk.-strain of toxoplasma.

Apparently the child suffered from retino-encephalopathy at a very early stage in its life.

CASE 5 [1]) : E. B., a girl is born 22nd May 1946.

SUMMARY : Hydrocephalus was observed in this child even a few days after birth. The child was admitted to hospital on the thirteenth day after delivery being off her food and having attacks of cyanosis. There appears to be situs inversus totalis. The size of the head increases rather rapidly. On a röntgenological examination being made, in addition to hydrocephalus, intracerebral calcifications are found to be present.

At the age of 6 weeks abnormalities in both eyes were noticed viz. : microphthalmy and iritis in the left eye and focal lesions in the right fundus. Hence the child manifests the clinical picture of infantile toxoplasmosis. An examination of the blood, lumbar and ventricular fluid, both direct and by intracerebral and intraperitoneal injections in mice, were negative. Toxoplasma neutralization tests with the serum of the child were invariably positive, both with respect to the Bk.-strain and with respect to the SABIN-strain of toxoplasmas. The toxoplasma

[1]) This case is going to be published in full by Prof. VAN CREVELD and Dr. ARONS.

neutralization test with the serum of the mother gave with respect to the SABIN-strain once a positive and once a doubtful result. The mother, shortly before the pregnancy of this child, was said to have had "typhus abdominalis" and at the commencement of the pregnancy, cholecystitis.

OPHTHALMOLOGIC EXAMINATION (27th October 1946) :

Both eyes make continual nystagmoid movements and are mainly directed downwards. The palpebral fissures are narrower than normally ; the left palpebral fissure is narrower than the right.

Right Eye : There is microphthalmy. The right cornea has a horizontal diameter of roughly 8 mm. The cornea is clear. The pupil dilates normally on the instillation of homatropine. The lens and vitreous are clear. In the fundus oculi there are focal lesions of a varying nature. There is an ill-defined, paracentrally situated, yellowish-white lesion projecting into the vitreous, roughly 4 disc diameters in size, and bordered by darkly pigmented lesions. There are some smaller, partially pigmented lesions, too. Temporally the retina is of a greyish-brown colour giving the impression of a detachment of the retina. There is therefore a focal, partly active, partly inactive chorioretinitis, with detachment of the retina. The papilla is sharply defined and greyish-white (atrophia papillae n. optici) (Plate II).

Left Eye : The left bulb is extremely small. The cornea horizontally measures only 5 mm. The cornea is clear. The pupil is narrow and fails to dilate on the instillation of homatropine. There are adhesions of the iris to the lens. The lens is clear. There are greyish-brown masses projecting into the vitreous. The lesions are presumably of the same nature as in the right fundus oculi.

Consequently there is a deviation of the eyes and nystagmus. There is a bilateral microphthalmy especially marked on the left side. In both the fundi there is a partially active chorioretinitis. The papilla nervi optici is pronouncedly atrophic on the right. Iritis is present in the left eye.

CASE 6 : P. DE C., a boy, born July 10th 1945, is known to be suffering from convulsions and increasing size of the head since the first month of life. A re-examination at the age of $1\frac{1}{2}$ years revealed a healed chorioretinal lesion in the right eye.

FAMILY HISTORY : It is the second child of a healthy father and mother. There was no trouble during pregnancy. The first child is normal, the third one was a still-born child. A post-mortem examination was made, but unfortunately the result of the examination is not known.

The toxoplasma neutralization test with the serum of the mother is positive with respect to the Sabin-strain of toxoplasma.

PERSONAL HISTORY : The boy was a full-term one and was born normally. Even at the early age of 6 weeks, the mother was struck by the "absent" look of the child and the "unresponsiveness" of the eyes. At the age of 4 months, it had "fits" consisting of staring, squinting, spasms in the arms and legs and screaming. These fits lasted but a few seconds and were repeated as many as thirty times a day. The size of the head gradually increased.

The diagnosis was : hydrocephalus, congenital malformation of the brain, marked mental retardation.

PHYSICAL EXAMINATION : The size of the head at the age of $1\frac{1}{2}$ years measured 51 cm. The fontanel is wide open and measures 3 × 3 cm. The child's weight is 9.150 grammes. The internal organs reveal no abnormalities. The reflexes are, on account of the restless state of the child, not to be ascertained. PIRQUET's reaction is negative. The child is backward to a pronounced degree. At the age of 2 years the size of the head is 53 cm. The child is very strong and wild having a healthy appearance. It sleeps very little and only cries when it is hungry. It has not yet learned to sit up.

LABORATORY DATA : There are no abnormalities in the urine.

Examination of the Blood : The sedimentation rate is normal.

Examination of the Spinal Fluid : NONNE-APELT's reaction is negative. There are no cells in the spinal fluid. The sugar content amounts to 82 mgr.%.

OPHTHALMOLOGICAL EXAMINATION : The child does not react to objects, but it does react to light. Both eyes are about normal size, the right eye, however, gives the impression of being somewhat smaller than the left. Convergent strabismus is present.

Right eye : The iris shows no abnormalities. The pupil reacts to light and on the instillation of atropine becomes moderately dilated. The media are clear.

Fundus oculi : In the macular area there is an almost round, healed chorioretinitic lesion approx. 4 to 5 disc diameters in size. In the centre of the lesion is a pigmentation. On the nasal side of the papilla there is a focal choroidal atrophy a good 1 disc diameter in size. There are a few scattered smaller old inflammatory lesions here and there in the fundus, partially pigmented. The papilla is of a grey-pink colour and on the temporal side somewhat pale (Plate II).

Left eye : The iris is normal, the pupil reacts to light and after the instillation of atropine becomes moderately dilated. The media are clear.

Fundus oculi : The papilla is slightly pale ; for the rest the fundus oculi is quite normal.

RÖNTGENOLOGICAL EXAMINATION OF THE SKULL : There is a marked hydrocephalus, but there are no calcium shadows visible.

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. Inoculation with the spinal fluid caused no toxoplasmosis in animals. The spinal fluid was kept at room temperature and only after some considerable time after the puncture was it injected. It is possible that this had an effect on the result obtained.
B. The serum neutralization test is positive with respect to the Sabin-strain of toxoplasma.

SUMMARY : A boy suffers from convulsions, a steadily increasing size of the head and mental retardation from the first months of life. Blindness was discovered at the age of 6 weeks. When the child was $1\frac{1}{2}$ years old, several healed chorioretinal lesions were revealed on an ophthalmologic examination and also the presence of bilateral atrophy of the optic nerve head, convergent squint and probable slight microphthalmia of the right eye. After the discovery of the

fundus lesions the diagnosis of congenital malformations of the brain had to be changed into probably congenital retino-encephalopathy in the inactive stage.

Parasitological examination of the spinal fluid failed to establish the diagnosis of toxoplasmosis.

The toxoplasma neutralization tests with the serum of both child and mother were positive with respect to the SABIN-strain of toxoplasma.

The mother gave birth to another child that was still-born after a seven months' pregnancy. Unfortunately autopsy findings are not available.

CASE 7 [1]) : H. W., a girl is born 18th August 1946.

SUMMARY : Soon after birth a grey reflex from both pupils was observed in this girl. After the first month of life progressive hydrocephalus was revealed. The child began to refuse food and started vomiting. Though distinct neurological disorders were absent, the muscles seemed to be hypertonic and sometimes the extremities trembled. The cerebrospinal fluid was always clear and became slightly xanthochromic in the course of the disease. A high protein content was mostly found in association with a normal or slightly increased cell content. On the X-ray photos of the skull calcifications are visible in the brein-tissue, symmetrically localized and presumably associated with the lateral ventricles. Only the right ventricle fills with air in ventriculography and is considerably dilated. The air introduced causes a "honeycomb pattern" of the ventricle. There is hypochromic anemia and leukocytosis.

On an examination of the eyes, there appeared to be, among other things, extensive bilateral retinal lesions. Consequently the child manifested a syndrome of retino-encephalopathy, which, in this case, is without much doubt of a congenital nature.

Ventricular fluid was injected intracerebrally in mice and guinea-pigs on several occasions, however with a negative result.

The toxoplasma neutralization test with the serum of the child, both with respect to the Bk.-strain and to the SABIN-strain is positive. With the serum of the mother, the neutralization test with respect to the Bk.-strain is positive, to the SABIN-strain is doubtful. A neutralization test made with the cerebrospinal fluid of the child

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[1]) This case will be published in full by Prof. VAN LOOKEREN CAMPAGNE and Dr. ENGELHARDT.

with respect to the Bk.-strain is positive, with respect to the SABIN-strain, is doubtful.

The mother limps. She is said to have suffered from "poliomyelitis" in her youth. Her first child died at the age of 6 weeks from "exsiccation". Once she had a miscarriage after a 2½-month-pregnancy. The patient is her second child.

OPHTHALMOLOGIC EXAMINATION (9th November 1947): The child fails to react to light. The eyes are continually on the move. The palpebral fissures are very narrow. Both eyes are very small.

Right Eye: The horizontal diameter of the cornea measures 7½ mm. The cornea is slightly deformed. The pupil is narrow and enlarges on the instillation of atropine but moderately. Adhesions of the iris to the lens exist. In a dilated state the pupil is not quite round and lies somewhat eccentrically (Fig. 8). All the media are clear. Of the fundus oculi it is not difficult to form an opinion.

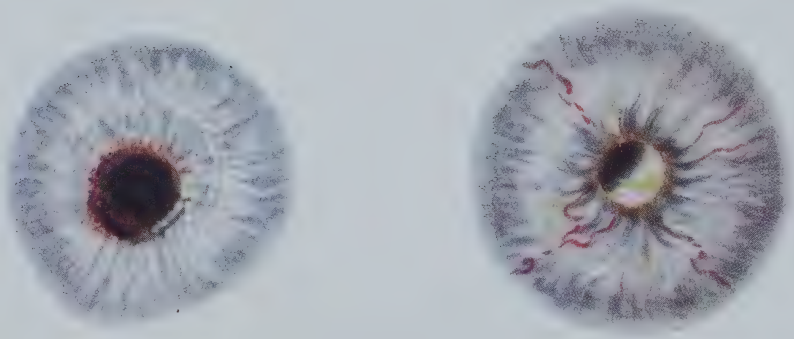
On the nasal side the normal fundus-reflex is present, while on the temporal side there is a grey-white reflex. It appears to be a greyish-white inflammatory mass lying to some extent sub-retinally and partly in the retina, projecting into the vitreous about 10 diopters and accompanied by sub-retinal exudate. The detachment of the retina so formed, is bordered by a band of pigment and a zone of chorioretinal atrophy giving the nasal portion of the fundus a coarse pepper and salt appearance. The papilla is not visible. There is very little left of the retinal vessels. The changes surrounding the lesion look exactly like the so-called "high water mark" (Plate III).

Left Eye: The horizontal measurement of the cornea amounts to 8½ mm. The cornea is clear. The anterior chamber is shallower than the right. The iris is arched forward (iris bombans). The contents of the anterior chamber is somewhat opalescent. The pupil fails to enlarge on atropine. There is a total adhesion of the pupillary border to the lens. Blood-vessels are visible even macroscopically in the iris. The lens nasally is only slightly hazy, whereas temporally there is an intense yellowish-white opacity (Fig. 8). Through the nasal part of the lens there is a grey reflex to be perceived from the vitreous, without any details being observed however. In the fundus oculi there are presumably changes of the same nature as in the right eye.

So in the case of this child there is a strongly pronounced microphthalmy and enophthalmy on both sides. Iritis is present in both eyes. In the left eye there is a partial cataract. In both eyes there is a so-called pseudo-glioma caused by an inflammatory tumour with secondary retinal detachment.

CASE 8: A. N., a girl was born 30th January 1947. The mother consulted an ophthalmologist when the child was only 5 weeks old, because the "child had such small eyes and was probably blind".

FAMILY HISTORY: Both parents of the child are healthy. The mother has given birth to two other children, both being normal. She has never had a miscarriage. Four weeks prior to delivery she had an influenza-like infection for a few days. There was a dog and a cat in the house. The WASSERMANN test, both in the blood of the mother and the father is negative. The toxoplasma neutralization test with the serum of the mother is positive, both with respect to the Bk.-strain and to the SABIN-strain.



Right eye Left eye

Fig. 8 : Case 7. Iritis associated with positive serum neutralization test for toxoplasmosis. Microphthalmia (horizontal diameter of the cornea : right eye $7\frac{1}{2}$ mm, left eye $8\frac{1}{2}$ mm). Cataract in the left eye.

Fig. 9 : Case 8. Hydrocephalia.

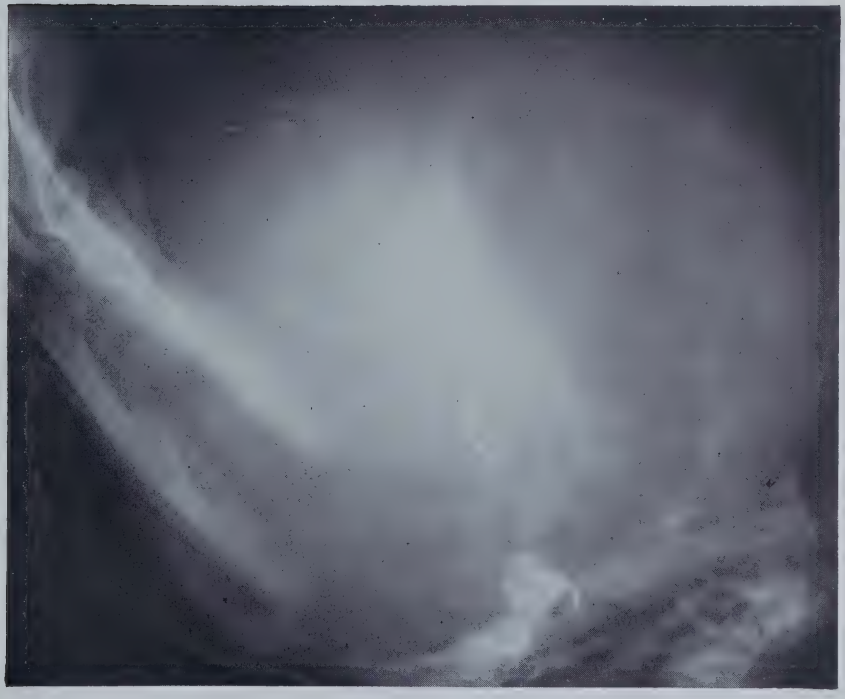
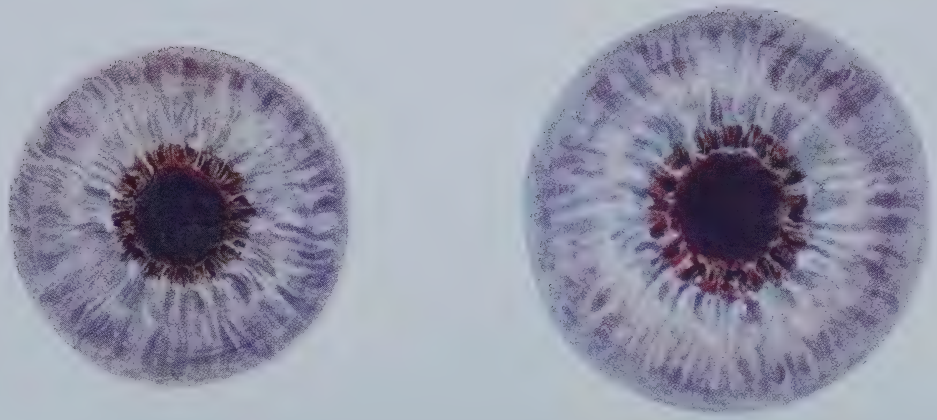


Fig. 10 : Case 8. Hydrocephalia. Cerebral calcification.
"Honeycomb-pattern" of dilated, air-filled lateral ventricle.



Right eye

Left eye

Fig. 11 : Case 8. Iritis associated with positive serum neutralization test for toxoplasmosis. Microphthalmia (horizontal diameter of the cornea : right eye 8 mm, left eye $9\frac{1}{2}$ mm).

PERSONAL HISTORY : The girl was a full-term one and was born normally. Her weight at birth amounted to 2.500 grammes. Even directly after birth, it struck the mother that the child had a large head and that its eyes were small. This made her consult an ophthalmologist when the child was 5 weeks old. The child took its food well, grew well and was "lively". It has never shown any convulsions.

OPHTHALMOLOGICAL EXAMINATION : Both eyes are continually showing nystagmoid movements and are mostly directed to the left and downward. There is convergent strabismus present.

Right Eye : The right palpebral fissure and the right eye are abnormally small. The horizontal diameter of the cornea measures 8 mm. The cornea is clear. The pupil is narrow showing no reaction to light and dilates but little on atropine. When dilated adhesions of the iris to the lens and the presence of "fibrin" on the surface of the lens are visible. The iris is of a dirty bluish-grey colour (Fig. 11). The vitreous is clear. Fundoscopic examination is difficult.

The fundus lightens inferonasally with a normal red colour, while a few retinal vessels are visible. Superotemporally the fundus-reflex is not red but green-brown, caused by masses projecting into the vitreous. In a few places the lesion is bordered by a white atrophic zone. This gives the impression that, in this eye, intensely pigmented inflammatory masses are present. The papilla is not to be found (Plate III).

Left Eye : The left palpebral fissure and the left eye are likewise smaller than the normal. The horizontal diameter of the cornea measures 9½ mm. The pupil is narrow, does not react to light and on the instillation of atropine is moderately dilated. Here, too, there appears to be adhesions of the dirty-blue-grey iris to the lens (Fig. 11). The lens is clear. There are some cloudy patches in the vitreous. The fundus oculi shows the following picture : The papilla is somewhat pale and ill-defined. Between the vena temporalis superior and inferior there is a loop-shaped anastomosis. In the macular region there is an oval atrophic lesion measuring 3 to 4 disc diameters. There are some choroidal vessels visible in the lesion. The centre of the lesion is slightly pigmented (Plate III).

RÖNTGENOLOGIC EXAMINATION OF THE SKULL : There appears to be calcium-shadows present in the brain (Fig. 10).

PHYSICAL EXAMINATION AND COURSE : At the age of 4 months the circumference of the head measured 56 cm. The fontanel is very large and the cranial sutures are considerably widened. The condition of the child is moderately good. The weight of the child is 6.900 gm. The heart and the lungs reveal no abnormalities. The spleen is just palpable. The reflexes are clonic. PIRQUET's reaction is negative.

Notwithstanding repeated ventricular puncturings and injections with glucose and magnesium-sulfate, the head gradually grew in size. The circumference of the head increased approx. 1 cm. per week (Fig. 9). No change takes place in the fundus picture.

LABORATORY DATA : There are no abnormalities in the urine.

Examination of the Blood : the content of hemoglobine amounts to 14 gr.%. Erythrocytes 6.200.000. Leukocytes 15.200 : polymorphonuclear leukocytes 59 %, lymphocytes 36 %, monocytes 4 %, metamyelocytes 1 %. The sedimentation rate is normal (5/14). The WASSERMANN and MEINICKE tests are negative.

Examination of the Spinal Fluid : The cerebrospinal fluid is clear and bacteriologically sterile. The WASSERMANN and MEINICKE tests are negative. The pressure

of the lumbar fluid amounts to 15 cm., of the ventricular fluid 70 cm. The number of cells in the lumbar fluid has increased (35-80/3), in the ventricular fluid the number amounts to 4-11/3. The NONNE test in the lumbar fluid is negative, the PANDY test being positive, while the sugar content amounts to 57 mgr.% (the blood-level being 127 mgr.%).

VENTRICULOGRAPHY : The left ventricle fills with air and appears to be considerably dilated. The right ventricle fails to fill with air. The air introduced into the ventricle causes a "honey-comb pattern". From the ventriculographic findings and from the different results in lumbar and ventricular puncturing, there appears to be non-communicating hydrocephalus (Fig. 10).

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :
A. Intracerebral inoculation of three guinea-pigs had a negative result.
B. Serum neutralization test (with respect to the Bk.-strain) : positive.

SUMMARY : A full-term, normally born girl has suffered from progressive hydrocephalus from birth. The mother consulted an ophthalmologist when the child was 5 weeks old because the eyes were small and the child could not see. There is convergent strabismus, nystagmus and deviation of the eyes. There is bilateral microphthalmy. Iritis and chorioretinitis is present in both eyes. In the right fundus the papilla is not visible, in the left eye there is mild papillary atrophy. A röntgenologic examination of the skull revealed, besides a marked hydrocephalus, several calcium shadows in the brain. There is a left-sided non-communicating internal hydrocephalus. In the lumbar fluid there is a moderate increase in the number of cells and the Pandy test is positive. Apparently the child is suffering from a congenital retino-encephalopathy.

No toxoplasmas were to be found in the cerebrospinal fluid by animal inoculation. Neutralization tests for toxoplasmosis with the serum of both the child and the mother had a positive result, with the serum of the mother with respect to both the Bk.-strain and the SABIN-strain, with the serum of the child with respect to the Bk.-strain of toxoplasma.

CASE 9 : M. KL., a girl, born 4th April 1937 came under observation for poor vision of the right eye when she was nine years old.

FAMILY HISTORY : The mother has never been ill. There was no trouble during pregnancy. A younger brother is normal. The patient is a second child. Six years later there was a still-born, full-term child. There has always been a cat, a dog and some rabbits in the house.

The toxoplasma neutralization test with the serum of the mother is, with respect to the SABIN-strain, positive.

PERSONAL HISTORY : The child was born normally and cried at once. At the age of 1½ years, it had one convulsion, which was never repeated. During its fifth year a slight squint of the right eye was noted. When the child began school, it was discovered that it could not see well with the right eye.

PHYSICAL EXAMINATION : The internal organs reveal no abnormalities. PIRQUET's reaction is negative. The WASSERMANN and SACHS-GEORGI as well as the KLINE test with the blood are negative.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : The impressiones digitatae are too pronounced for the age of the child. Abnormal shadows are not present.

OPHTHALMOLOGIC EXAMINATION : There is a slight divergent and sursumvergent strabismus of the right eye. The movements of the eyes are undisturbed. The visual acuity of the right eye amounts to 3/60, of the left eye is 6/6. The eyes are of normal size and manifest no external abnormalities. The media are clear. In the right fundus there is, in the macular region, an inactive chorioretinitic lesion two to three disc diameters in size and a smaller one above it. In the centre of the lesion there is a very little projecting, greyish-red "disc", roughly 1 disc diameter in size, surrounded by a narrow border of pigment and by an atrophic zone which is divided into sectors by thin lines of pigment. Between the papilla and the central lesion there is a pepper and salt fundus.

The papilla is pale. The retinal vessels are normal. A blood-vessel traverses the central lesion, being partially covered by inflammatory tissue (Plate III).

TOXOPLASMA NEUTRALIZATION TEST : With respect to the SABIN-strain, the serum of the child yielded a positive neutralization test.

SUMMARY : A healed central chorioretinal lesion was discovered in one eye of a nine-year-old girl. The optic disc was pale. There is a slight divergent and sursumvergent squint of the right eye. The child has had one fit of convulsions and that when she was 1½ years old. On the X-ray photograph of the skull marked impressiones were present but no calcifications. Toxoplasma neutralization tests with the serum of both the child and the mother, with respect to the SABIN-strain, were positive.

CASE 10 : G. v. BR., a boy, born 1934, is known to have inactive chorioretinal lesions in both eyes since he was 6 years old. He was re-examined at the age of 13.

FAMILY HISTORY : This boy is the youngest of 8 children. All the other children are normal. During pregnancy the mother had to go on diet and take much rest on account of a high blood-pressure, but was otherwise never ill. She had a 2 months miscarriage after the fifth child. After the birth of the patient she had three still-born, full-term children in succession. They have never kept any domestic animals.

PERSONAL HISTORY : The boy had a normal birth. His physical and mental development were normal, and has never had any fits of convulsions. Even when he was 8 months old his mother says he occasionally looked cross-eyed. The school-doctor discovered that the function of the right eye was defective, when the boy was 6 years old.

OPHTHALMOLOGIC EXAMINATION : The eyes show no external abnormalities. The visual acuity of the right eye amounts to 1,5/10, that of the left eye 10/10. The refraction on both sides is $1\frac{1}{2}$ diopters hypermetropic.

Ophthalmoscopic Examination : In the right fundus there are one large and 2 smaller, centrally situated, inactive, chorioretinal lesions. The largest one is roughly 3 to 5 disc diameters in size, is somewhat depressed and the temporal part is darkly pigmented. A similar smaller lesion a good 1 disc diameter in size is found above these, while besides this, a still smaller darkly pigmented lesion is also present. In the lesions there are a few choroidal blood-vessels visible. The retinal vessels traverse the lesions. The temporal sector of the papilla is pale (Plate III).

In the left fundus there are superonasally to the papilla two large healed chorioretinal lesions cir. 4 to 5 disc diameters and a few small specks of pigment. In both lesions there are greyish-pink, somewhat elevated, darkly pigmented "discs", surrounded by atrophic zones. The papilla is normal. The retinal vessels traverse the lesions (Plate III).

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : No abnormalities.

TOXOPLASMA NEUTRALIZATION TEST : With respect to the SABIN-strain, the serum yielded a positive result.

SUMMARY : Several larger and a few smaller healed chorioretinal lesions were discovered in an otherwise healthy boy of 6 years. There is a slight temporal papillary atrophy in the right eye. The toxoplasma neutralization test with the serum of this boy, made at the age of 13 years, proved, with respect to the SABIN-strain, to be positive.

CASE 11 [1]) : J. S., a girl, born in 1940, was known to have inactive central chorioretinal lesions in both eyes even during the first year of life and probably of congenital origin. She was re-examined when she was 6 years old.

FAMILY HISTORY : The mother suffered from severe recurrent papillo-retinitis and cyclitis in the left eye when she was 26 years old (in 1939). This was the year preceding the birth of the patient. She was hospitalized during several months. The cause of the inflammation could not be determined. PIRQUET's reaction was positive but there were no indications as to a tuberculous etiology. The inflammation subsided gradually resulting in extensive chorioretinal scars with scattered pigment spots throughout the whole posterior pole of the eye as well as in atrophy of the optic nerve. In 1942 a few small inactive chorioretinal lesions were noted in the right eye as well. In October

[1]) BINKHORST (2, 3).

1947 the toxoplasma neutralization test with the serum of the mother gave a doubtful result with regard to the Bk.-strain.

The mother has two other children, one of which suffered from recurrent retrobulbar neuritis at the age of 9 years (in 1942). The etiology again remained unknown. A striking eosinophilia was present in the blood. Unfortunately the toxoplasma neutralization test with the serum of this girl could not be done.

After the birth of the patient the mother gave birth to 2 normal children. She never had miscarriages.

PERSONAL HISTORY : The mother noted that the child's eyes were defective when it was five months old. At this time there were already nystagmus, convergent strabismus and the same fundus lesions as stated hereafter. The diagnosis ran : "choroiditis or macular coloboma". There were no more changes later on in the fundi. In other aspects the child developed normally.

OPHTHALMOLOGIC EXAMINATION : There is rotatory nystagmus and alternating convergent strabismus. Both eyes are small (microphthalmy) ; the horizontal measurement of the cornea amounts to 10 mm. on both sides. The pupils react normally and are normal in shape. The visual acuity of the right eye after correction amounts to 1/20, that of the left eye 1/6. The refraction is myopic, horizontally 5 diopters and vertically 10 diopters. The child fixes eccentrically. The media are clear. In both macular regions there is an almost round, inactive, chorioretinal lesion, roughly 5 disc diameters in size. The choroid and the retina are atrophic to a marked degree in this area, dark pigmentation being present especially at the border of the lesion. In the right fundus some additional small lesions are present (Plate IV).

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : No abnormalities.

TOXOPLASMA NEUTRALIZATION TEST (with regard to the Bk.-strain) : positive.

SUMMARY : Healed lesions in both macular areas, probably of congenital origin were noted in a 5-month-old child. No changes developed in these lesions during 6 years.

Ophthalmologic examination at the age of 6 revealed bilateral slight microphthalmia, alternant convergent squint, nystagmus, myopic refraction and inactive chorioretinal lesions in the macular area. The toxoplasma neutralization test with the serum of the patient was positive with respect to the Bk.-strain.

The mother of the child had a severe papillo-retinitis and cyclitis of unknown etiology in the year preceding the birth of the child. The toxoplasma neutralization test with the serum of the mother was doubtful with respect to the Bk.-strain. An elder sister of the patient suffered from retrobulbar neuritis.

CASE 12 : H. M., born in 1928. The boy complained of spots before the left eye when he was about 7 years old. At the age of 13 he consulted an ophthalmologist, who found several active and inactive chorioretinal

lesions in the left eye. The last examination was made when the boy was 19.

FAMILY HISTORY : Both parents have always been healthy. The mother has never had a miscarriage nor still-born children. A younger sister is normal. There has been no tuberculosis in the family.

The toxoplasma neutralization test with the serum of the mother, with respect to the SABIN-strain, is positive.

PERSONAL HISTORY : The birth was a normal one. The boy has had no illness of any significance, neither has he had any fits of convulsions. When he was 7 years old he observed a sort of „veil" before his left eye which got more pronounced later on. He has never complained of his right eye. At the age of 13 several active and inactive chorioretinal lesions were noted in the left eye accompanied by opacities of the vitreous. The cause of this inflammation could not be detected. A physical and röntgenological examination of the internal organs was completely negative and laboratory examinations equally so. The WASSERMANN test was negative. PIRQUET's reaction was negative. No foci of inflammation could be detected by an otorhinologic examination. Aspecific therapy was given.

A fresh parapapillary lesion occurred at the age of fifteen years. Another examination did not assist in the diagnosis. PIRQUET's reaction was again negative. The sedimentation rate of the red blood-cells amounted to 10/25. The process became inactive again.

OPHTHALMOLOGIC EXAMINATION : Besides a mild chronic conjunctivitis, the eyes show no external abnormalities. The pupils are equal in size and react normally. The visual acuity of both eyes respectively are 6/4,5. The media are clear. The right fundus oculi is normal. In the left fundus there are inferonasally to the papilla three inactive, pigmented, inflammatory lesions 1 to 2 disc diameters in size, as well as a few smaller specks of pigment. One lesion has a conical, grey-coloured off-shoot along the vena nasalis inferior. In the vitreous there are a few small grey cloudy patches bound to the parapapillary lesion by fine threads. The nasal half of the papilla is covered by a thin membrane stretching between the inferior and superior vascular stem. The papilla is otherwise normal. Surrounding the papilla there are a few specks of pigment in a depigmented zone. The vessels in the retina are normal, also across the lesions (Plate IV).

X-RAY EXAMINATION OF THE SKULL : No abnormalities.

TOXOPLASMA NEUTRALIZATION TEST : With respect to the SABIN-strain, the serum has a neutralizing effect.

SUMMARY : A youth now 19 years old and his mother both yield a positive neutralization test against toxoplasma. The youth has been suffering from unilateral, recurring, focal chorioretinitis since his childhood days.

CASE 13 : Mrs. v. SCH.-BR., a 53-year-old woman, born in 1893, came under observation on account of presbyobia.

FAMILY HISTORY : The patient had glasses + 1 sph. for a considerable time, but these failed to suit her of late. She used to have good eyes. She has complained of headaches all her life. She has never had any particular illness. She has three healthy daughters, 2 of which have one healthy child each. She has never had a miscarriage. Her husband is a blacksmith and is healthy. The patient is very fond of animals and has always had a dog, a cat, fowls and pigs and in the war years had rabbits. At the end of 1944 she had a very sick cat ; the head was "blue" and "looked dirty", the eyes were "hazy" and the animal had convulsions. The cat was killed.

OPHTHALMOLOGIC EXAMINATION AND COURSE (28th May 1946) : The visual acuity amounts on both sides to 6/6 ; with + 1½ sph. Snellen optotypes D = 0.5 are read. The ocular tension is normal. The media are clear. Ophthalmoscopically the right fundus is normal. In the left fundus between the papilla and the fovea centralis there is a grey, not very sharply defined, swollen area in the retina approximately 1 disc diameter in size. The lesion is surrounded by retinal hemorrhages. It was not possible to make a diagnosis. The possibility of an affection of the blood-vessels, of an inflammation and of a neoplasm was entertained. The papilla and the retinal vessels appeared to be normal (Plate IV).

Little change came in the picture during the further period of observation and this very slowly. The hemorrhages around the lesion varied in size. The extension of the hemorrhages up to the fovea centralis caused a sudden deterioration of the visual acuity to 6/18 some months later, a year after this even to 0.5/60. Then the visual acuity recovered again partially. A zone of depigmentation gradually arose round the lesion.

19th March 1948 : The visual acuity of the left eye amounts to 6/18. Ophthalmoscopically there is no abnormality in the right fundus. In the left fundus the lesion is slightly elevated,fairly well-defined, diamond-shaped, of a greyish-brown colour and about 1 disc diameter in size. At the border of the lesion the colour is dark-brown in places. There are still a few hemorrhages around the lesion and there is a zone of depigmentation reaching into the macula. The papilla and the retinal vessels show no abnormalities (Plate IV).

Slit-lamp Examination : There are a number of minute brown precipitates against the posterior surface of the left cornea. In the anterior chamber there are a few scattered particles. For the rest, iris, lens and vitreous show no abnormalities.

An absolute scotoma is present in the left eye approximately 1½ × the size of the blind spot, corresponding to the fundus-lesion.

PHYSICAL EXAMINATION AND LABORATORY DATA : The patient has a varying degree of high blood-pressure. The heart, the lungs and abdominal organs show no abnormalities. The spleen and liver are somewhat enlarged. PIRQUET's reaction is negative. A röntgenographic examination of the lungs shows no abnormalities.

Examination of the blood : The content of hemoglobin amounts to 12 grams. Erythrocytes 5.120.000. Leukocytes 3.700 : formula normal. The sedimentation rate has increased (20/35).

Analysis of Urine : There is a trace of albumin in the urine. The melanin test was weakly positive twice.

TOXOPLASMA NEUTRALIZATION TEST : The rabbit skin test with the serum is positive with respect to the SABIN-strain of toxoplasma.

SUMMARY : In the case of a 53-year-old woman a focal lesion is detected by chance in the left fundus oculi between the papilla nervi optici and the fovea centralis. It is a grey-coloured swelling of the retina, not very sharply defined, approx. 1 disc diameter in size and surrounded by hemorrhages in the retina. In the course of almost two years only a very gradual change has taken place ; the grey-coloured centre is more sharply defined and is bordered by pigment in places. There are still hemorrhages around the lesion and a zone of depigmentation has arisen, reaching into the macula and causing a diminution in the visual acuity. We get the impression of an extremely chronic, inflammatory process. There is a weakly positive melanin reaction in the urine. The toxoplasma neutralization test with the serum is positive with respect to the SABIN-strain of toxoplasma.

Some time prior to the discovery of the fundus lesion, the domestic cat had fallen ill.

III. RETINO-ENCEPHALOPATHY OF UNDETERMINED ETIOLOGY WITH CLINICAL RESEMBLANCE TO TOXOPLASMIC RETINO-ENCEPHALOPATHY (CASES 14 TO 20 INCLUSIVE)

The cases 14 to 20 inclusive have as common characteristics the presence of fundus lesions together with cerebral symptoms, which we may assume are the sequelae of a retino-encephalopathy. The ages vary from 1 to 27 years.

CASE 14 : H. T., a boy, born 2nd Jan. 1932, was re-examined when he was 15 years old. Healed fundus lesions were known to be present from the 4th year of life.

FAMILY HISTORY : The boy is a twin. The mother has always been healthy and has never had a miscarriage. She has 8 children, one child of which was born before, and 5 children after the patient. There was no trouble during pregnancy. All the other children are healthy ; they have no ocular abnormalities, neither has the mother. The twin-sister has convergent strabismus. The X-ray photograph of the skull of the mother shows pronouncedly thick bones, without, however, there being any question of hyperostosis. On the X-ray photograph of the skull of the twin-sister there are some shadows of calcium-density visible.

The toxoplasma neutralization test with respect to the SABIN-strain is negative with the serum of the mother and doubtful with the serum of the twin-sister. During pregnancy a dog, pigeons and fowls were kept.

PERSONAL HISTORY : The birth of the twins went off quite normally. When the boy was two months old, the mother had already observed that the eyes were not normal.

The eyes „quivered" continually and the child was always holding its hands before its eyes. Otherwise the child was as sound as a bell, grew well and its physical development was the same as that of his twin-sister. The child was not troublesome at all during the first few years. Later on, however, a marked motoric restlessness developed and he destroyed everything he could lay his hands on. At the age of 4 he had fits of convulsions. Since then he has been cared for in an institution. Fundus lesions were discovered for the first time at this age, which were diagnosed as "macular coloboma". Since that time the lesions have undergone no change.

OPHTHALMOLOGIC EXAMINATION : The boy's vision is poor. He has difficulty in fixing objects, soon losing sight of them again. Fixation is mostly effected with the right eye and the objects are held very close. There is a constant nystagmoid movement of the eyes. The left eye shows slight convergent strabismus. The pupils react normally. The visual acuity on the right is 1/12, on the left 0.5/60.

Right Eye : The right eye and the right cornea are of normal size. The horizontal measurement of the cornea amounts to 11 mm. The pupil dilates to the maximum on the instillation of homatropine. There are no synechiae posteriores. All the media are clear. The eye is 6 diopters myopic. In the fundus oculi there is a central, round, dark-pigmented, old inflammatory lesion measuring approx. 3 disc diameters. Here the choroid is almost completely atrophic and only a single choroidal blood-vessel is visible. The papilla is normal in colour. The course of the retinal vessels in the vicinity of the papilla is abnormal. We get the impression that the vessels have been drawn in the direction of the inflammatory lesion (Plate V).

Left Eye : The horizontal diameter of the cornea measures 9½ mm. The left eye is smaller than the right. The pupil dilates on the instillation of homatropine to its maximum. There are no synechiae posteriores. The media are clear. The eye is about 10 diopters myopic. In the fundus oculi there is a large, central, focal lesion consisting of a dirty-greyish coloured, somewhat elevated, triangular, tumour-like mass, surrounded by a dense band of pigment and, for the greater part on the nasal side, bordered by an area of choroidal atrophy including the papilla. Inferonasally to the papilla there is a small, greyish-coloured lesion with a band of pigment. The papilla is not sharply defined and is pale. The retinal vessels are narrow and show atypical course (Plate V).

RÖNTGENOGRAPHIC EXAMINATION : There are no intracerebral calcifications visible.

PHYSICAL EXAMINATION, MENTAL DEVELOPMENT AND LABORATORY DATA : The boy is physically robust. There is a pronounced mental retardation ; his behaviour, speech and intellectual powers are equal to those of a child of 8 (intelligence test of BINET-SIMON). The boy is continually making stereotyped movements.

Oto-rhinologic Examination : No abnormalities.

Internal Organs : There is a faint systolic souffle audible all over the heart. In the throat there are a few palpable lymph-nodes. Otherwise the internal organs manifest no abnormalities.

Neurologic Examination : No abnormalities. The reflexes are normal.

Laboratory Data : Examination of the Blood : The hemoglobin content is 70 %. Erythrocytes 3.840.000. Leukocytes 7.600 : eosinophils 1 %, polymorphonuclear leukocytes 42 %, lymphocytes 56 %, monocytes 1 %. The WASSERMANN and SACHS-GEORGI tests as well as the KLINE test are negative.

Examination of the Spinal Fluid : Pressure is normal. The spinal fluid contains

no cells. The NONNE test and the PANDY test are negative. Glucose-content 68 mgr.%. The gold-sol and benzoin tests are normal.

TOXOPLASMA NEUTRALIZATION TEST : With respect to the SABIN-strain, the serum of the patient was negative twice ; with regard to the Bk.-strain, once doubtful.

SUMMARY : A twin, even at the age of a few months, gave the impression that its vision was poor. It had fits of convulsions and there was considerable motoric restlessness. At the age of 4, the diagnosis was : bilateral macular coloboma. On being re-examined at the age of 15, nystagmus, microphthalmia, convergent strabismus, myopia and large central, post-inflammatory, chorioretinal lesions in both fundi were noted. Except for a few swollen lymphnodes in the throat and a systolic souffle over the heart, there are no physical abnormalities. The examination of the blood and spinal fluid is negative. Mental development is markedly retarded. This patient therefore reveals the remnants of a retino-encephalopathy which arose very early in life.

The twin-sister suffers from convergent strabismus, while the X-ray photograph of the skull shows a few shadows of calcium density. In the case of the mother there is a striking thickness of the skull bones. It is quite possible that we are concerned here with a familiar affection.

The toxoplasma neutralization tests with respect to the SABIN-strain, with the serum of the mother and with the serum of the patient are negative, with the serum of the twin-sister doubtful ; whereas with respect to the Bk.-strain the test with the serum of the patient is doubtful.

CASE 15 : E. DE W., a girl, born 24th September 1938, was first examined at the age of 8 years because of poor vision of the left eye.

FAMILY HISTORY : The girl is the second of 5 children. An elder brother had appendicitis. A younger brother had transient paresis of the musculus peronaeus, when he was two years old. A younger sister has a HORNER's syndrome on the left side. As a child the mother was frail but healthy. There was no trouble during pregnancy. A brother of the mother had an affection of the lungs. The father of the child had pleuritis in 1945, but is now cured. For the rest there has been no sickness in the family. The toxoplasma neutralization test with the serum of the mother is negative with respect to the SABIN-strain.

PERSONAL HISTORY : The birth had a normal course. The child developed normally and was never ill. She has never had any convulsions. PIRQUET's reaction is negative. When she was eight, the school-doctor noted that the vision of the left eye was defective.

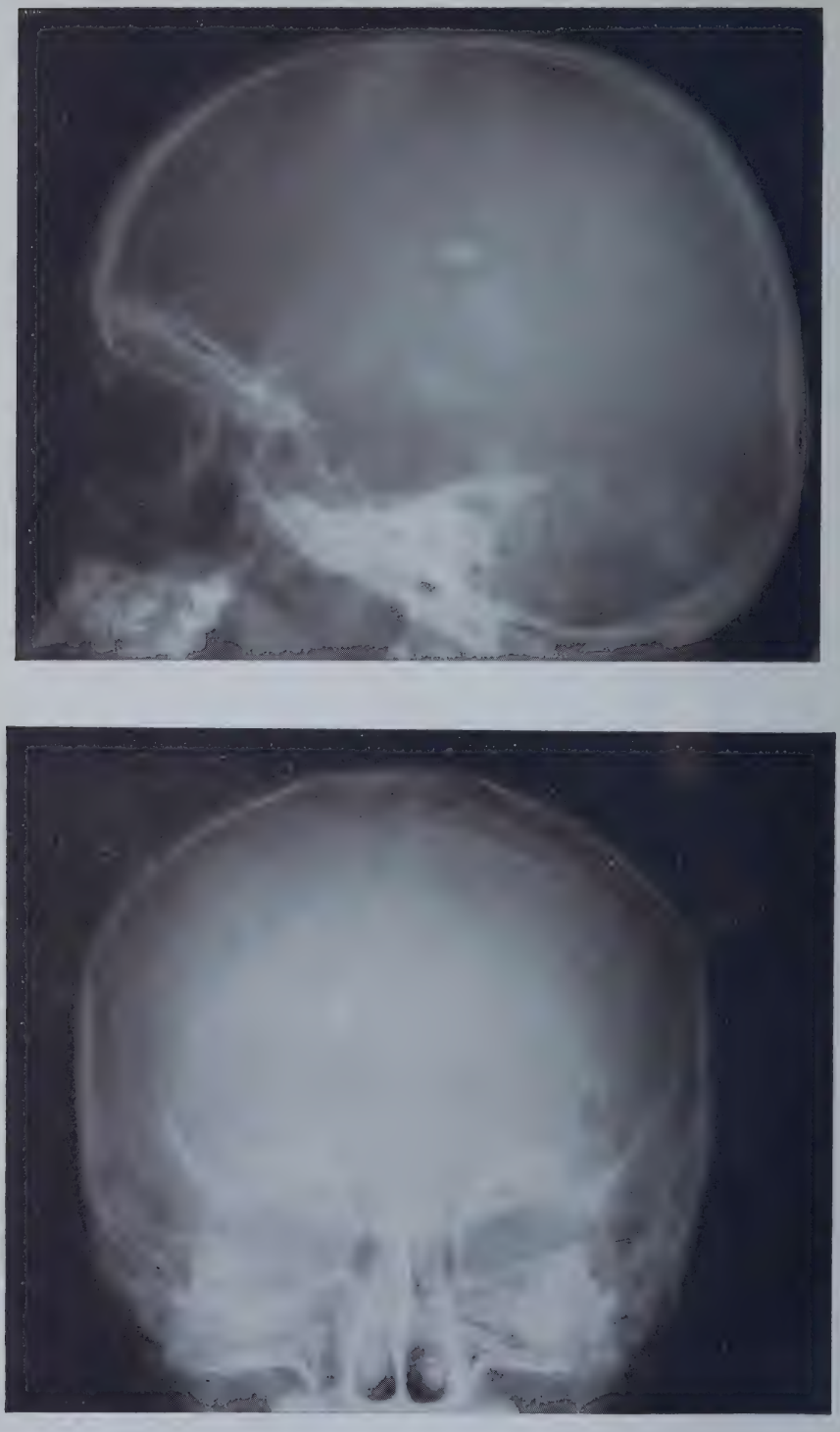


Fig. 12 : Case 15. Cerebral calcification.

OPHTHALMOLOGIC EXAMINATION : There are no external abnormalities of the eyes. The size of the eyes are normal. The pupils are equal and react normally. The visual acuity is : right 6/6 ; left 6/24. Refraction is $1\frac{1}{2}$ diopters hypermetropia on both sides. The media are clear. In both fundi there are, $\frac{1}{2}$ to 1 disc diameter inferotemporally to the fovea centralis, for a part intensely pigmented, slightly depressed chorioretinal lesions, fairly symmetrical in arrangement and appearance, and roughly 2 to 3 disc diameters in size. Moreover there is, in the right eye inferiorally, and in the left eye temporally, a small lesion. The papillae nervi optici are pale. The aspect and course of the retinal vessels are normal. The two central chorioretinal lesions are traversed by a few fine vascular branches (Plate V).

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : One single focus of intensive calcification is present in the brain-substance (Fig. 12).

TOXOPLASMA NEUTRALIZATION TEST : Negative with respect to the SABIN-strain.

SUMMARY : In an otherwise healthy 8-year-old girl bilateral healed chorioretinitis and bad vision in one eye was discovered. A röntgenographic examination of the skull revealed a focus of calcification in the brain. Serum neutralization tests for toxoplasmosis were negative, both in the girl and her mother, with respect to the SABIN-strain.

CASE 16 [1]) : A. B., a boy, born in 1929, was re-examined when he was 17 years old.

FAMILY HISTORY : The boy is the second child. Two other children are both normal. The mother had often complained of headaches during pregnancy. Abnormalities, however, were not found in her. In other members of the family there were no abnormalities of any importance either.

The toxoplasma neutralization test with the serum of the mother was negative with respect to the Bk.-strain of toxoplasma.

PERSONAL HISTORY : The child was born at full-term. The birth was a difficult one and the child did not cry at once. Even when he was only four weeks old, it was noticed that he rolled his eyes in a strange way. He was troublesome and was continuously crying. At the age of 5 months, during clinical observation for intestinal trouble, it was already ascertained that the child was mentally deficient. He learned to walk at the normal time. In speaking, however, he was backward. When he was a year and 9 months old he had a bad fit of convulsions, which were not repeated.

The first ophthalmological examination was made at the age of eight, when a bilateral healed chorioretinitis was revealed.

PHYSICAL EXAMINATION AND MENTAL DEVELOPMENT : There is a mild microcephalus. Otherwise physical development is normal. The mental development of this youth

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[1]) BINKHORST (2, 3).

of seventeen is equal to one of 5 years and 2 months (STANFORD-BINET intelligence test I), so that the intelligence-quotient amounts to 30 (imbecillitas).

The internal organs show no abnormalities. The syphilis tests in the blood are negative.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : Multiple small calcium-shadows are visible scattered about in the brain-substance.

OPHTHALMOLOGIC EXAMINATION : Convergent strabismus is present. Both eyes are normal in size. The movements of the eyes are normal. The media are clear on both sides. Both eyes are considerably myopic (approx. 10 diopters). The visual acuity on both sides after correction is 1/12.

Right fundus oculi : In the macular area there is a large, healed inflammatory lesion present six to seven disc diameters in size and more or less pear-shaped. There is an almost complete atrophy of the choroid, only a few blood-vessels of which are still visible. The pigmented epithelium is wholly atrophied, but in the centre and on the border of the lesion there is an accumulation of pigment. Somewhere about the centre of the lesion there is a somewhat elevated, greyish-brown mass presumably consisting of connective-tissue. In the vicinity of this large central lesion, there are a few small old chorioretinitic scars. The papilla nervi optici is greyish-white in colour and is bordered by a large crescent on the temporal side (Plate V).

Left fundus oculi : In the left eye, too, there is in the macular region an equally large lesion of post-inflammatory atrophy, almost round in shape and likewise with a nearly centrally located, greyish-brown, somewhat elevated tumor-like mass of connective-tissue. Streaks of pigment cause a sector-like division of the lesion. The papilla provided with a broad, temporal crescent is of a greyish-white colour here, too (Plate V).

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. Animal inoculation : 1st passage : 2 guinea-pigs and 3 mice are intracerebrally injected with spinal fluid. One mouse and one guinea-pig die after 26 and 29 days respectively after inoculation. A histological examination of these animals is negative. 2nd passage : 2 guinea-pigs and 3 mice are injected intracerebrally with the brains of the guinea-pigs that died spontaneously. One guinea-pig and one mouse died 7 and 9 days respectively after the injections. 3rd passage : One guinea-pig and 3 mice are injected intracerebrally with the brains of the two animals of the 2nd passage that died spontaneously. The animals show no reaction.
B. The neutralization test with the serum was with respect to the Bk.-strain negative and with respect to the SABIN-strain doubtful.

SUMMARY : A seventeen-year-old boy has developed abnormally since birth. A severe mental retardation appeared early in life. There was only one convulsion at the age of one year and 9 months. Convergent squint and nystagmoid movements of the eyes were noted as early as 4 months after birth. At the age of 8 years a bilateral healed central chorioretinitis and atrophy of the optic nerve head was noted. Both eyes are myopic. Multiple small calcium deposits are present in the brain.

Apparently the boy suffered from retino-encephalopathy in early life, the cause of which is still obscure. Neither parasites nor toxoplasma neutralizing anti-bodies were to be found in this case, neither were toxoplasma neutralizing anti-bodies encountered in the serum of the mother of the patient.

CASE 17 [1]) : B. L., a girl born in 1933, was re-examined at the age of 13 years.

FAMILY HISTORY : There had been no sickness or abnormalities in the family. The toxoplasma neutralization test with the serum of the mother is negative with respect to the Bk.-strain of toxoplasma.

PERSONAL HISTORY : The birth was a difficult one. Even shortly after birth the child had fits, at first very frequent (25—30 a day), gradually less often; during the last few years once or twice a month. Ever since her birth there had been a left-sided hemiplegia most pronounced in the arm. At first there was some development. Patient learned to sit up, acquired clean habits, learned to feed herself with a spoon and spoke a few words. When she was about 8, she learned to walk in a way. During the last few years, the child has been gradually getting worse and worse; she is getting more and more dazed.

Patient has had the measles, chicken-pox and erysipelas, otherwise she has had no illness of any importance.

PHYSICAL EXAMINATION AND MENTAL DEVELOPMENT : The girl is a torpid idiot. She does not speak. She is incontinent and helpless. Her interest in her environment is extremely slight. From time to time she gets into a mildly excited state, on which occasions she makes blowing noises and stereotype movements.

There is a left-sided spastic hemiplegia.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : No calcium shadows are visible.

OPHTHALMOLOGICAL EXAMINATION : Externally the eyes are normal. The media are clear. Right fundus oculi : In the immediate vicinity and bordering on the papilla there are three old chorioretinitic lesions measuring 1 to 2 disc diameter in size. Besides an atrophy of the pigmented epithelium, there is a local increase of pigment. The papilla is normal in colour (Plate VI).

Left fundus oculi : Supero-nasally to the papilla and surrounding it is an old chorioretinal lesion of the same nature as in the right fundus. Here, too, the papilla is of a normal colour (Plate VI).

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. Animal Inoculation. 3 mice and 3 guinea-pigs are intracerebrally inoculated with the centrifugated cerebrospinal fluid; 16 days after the inoculation all the animals are killed; histological examination negative.

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[1]) BINKHORST (2, 3).

B. Serum Neutralization Tests : The serum neutralization test was negative both with respect to the Bk.-strain and with respect to the SABIN-strain of toxoplasma.

SUMMARY : A 13-year-old girl was re-examined because of mental and neurologic disorder from birth. There is torpid idiocy and spastic hemiplegia of the extremities on the left side. The child has suffered from convulsions from birth. In both fundi healed lesions appeared to be present next to the optic nerve heads. These findings make it probable that above mentioned disorders are of an inflammatory origin. The child apparently suffers from retino-encephalopathy of the congenital type.

The cause is still unknown. The examination of the spinal fluid for toxoplasma was negative and serum tests for toxoplasma neutralizing anti-bodies were negative in both the patient and her mother.

CASE 18 [1]) : A. DE L., a boy, born in October 1946, was hospitalized at the age of 2 months.

FAMILY HISTORY : The parents of the child are healthy. The child is its mother's first. The mother has had no miscarriages. The course of pregnancy was a normal one. The toxoplasma neutralization test with the serum of the mother is positive with regard to the Bk.-strain, negative with respect to the SABIN-strain.

PERSONAL HISTORY : The child was a full-term one, and was born normally. During the first few weeks there were no special symptoms, but gradually the child went off its food. It struck the mother that the child was getting stiff.

PHYSICAL EXAMINATION AND COURSE : The nutritive condition on the whole is moderately good. Its weight is 4.200 grammes. There is distinct hypertonia of the muscles, especially of the lower extremities. The circumference of the head is 38 cm. The fontanel is 3 × 3 cm. in size. The mouth opens somewhat askew. With the exception of a few dry rhonchi in the lungs, the internal organs reveal no abnormalities. A few days after admission, the child suddenly had a high temperature caused by an intercurrent bronchitis and otitis media. The hypertonia continued, it being most pronounced in the lower extremities ; on account of spasm of the musculi adductores, the legs are stretched and crossed. During attacks the hypertonia increases and the child lies with its head thrown right back, its arms bent and its fists clenched. Mental development appears to be retarded ; at the age of 6 months the child had never laughed. It fails to react to light and is always groaning when not asleep. There is a pronounced lability of the body-temperature. The administration of sulfathiazole and penicillin has no effect on the temperature.

LABORATORY EXAMINATIONS : Examination of the Blood : The hemoglobin content is 87 %. Erythrocytes 4.400.000. Leukocytes 10.800 : polymorphonuclear leukocytes 37 %,

[1]) BRÜCKNER c.s.

myelocytes 1 %, monocytes 4 %, lymphocytes 58 %. There is a moderate toxic granulation of the leukocytes. The microsedimentation rate of the erythrocytes amounts to 15 mm. during the first hour. The WASSERMANN and SACHS-GEORGI tests are negative.

Examination of the Urine : The albumin-, glucose- and urobilin tests are negative. There are some leukocytes in the sediment.

Examination of the Spinal Fluid : The pressure of the lumbar fluid is normal. The NONNE test and the PANDY test are positive. The number of cells amounts to 90/3. The total protein content is 4.3 ‰ (globulin (ammonium-sulfate) T 55, globulin (ESBACH) T 10.5, albumin T 10.5, globulin-albumin-quotient 1). The gold-sol test and the benzoin test are pathologic to a marked degree. On a re-examination of the lumbar fluid, the number of cells are 49/3 and the total content of protein 1.64 ‰.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : There are no abnormalities.

OPHTHALMOLOGIC EXAMINATION : At the age of 2 months ocular abnormalities were noticed. Both eyes are pretty well identical. The eyes are pathologically small on both sides ; the horizontal diameter of the cornea on both sides measures roughly 6½ mm. The cornea is clear. The anterior chamber is of normal depth. The pupils are not quite round and fail to react to light ; there appears to be posterior synechiae on both sides. On the instillation of atropine, the pupils dilate very little and assume an irregular shape. In the vitreous there are some dense, cloudy patches on both sides which hampered the examination of the fundus oculi considerably. Yet the examination revealed a diffuse lesion in the fundi, especially in the vicinity of the papilla, consisting of grey-green masses projecting into the vitreous, presumably a result of an extensive diffuse retinitis. In the further course these ocular lesions have remained more or less stationary.

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. 2 Guinea-pigs were inoculated with the cerebrospinal fluid. The animals were killed after 7 weeks and a brain-emulsion was injected into 2 other guinea-pigs. These tests proved negative. It should be mentioned here that the examination was made after the child had received large doses of sulfathiazole and penicillin, which may have had some effect on the result.

B. Serum Neutralization Test. The serum of the child was examined to ascertain whether there were any toxoplasma neutralizing anti-bodies present, both with respect to the Bk.-strain and with regard to the SABIN-strain. The tests proved negative.

SUMMARY : A full-term and normally born boy showed, when only a few weeks old, a spasticity of the muscles which gradually increased, assuming more and more the nature of attacks accompanied by opisthotonos. In the further course of the sickness the child turned out to be mentally deficient. It fails to react to light. There is a labile body-temperature. On several occasions considerable changes in the spinal fluid were found : a marked increase in the protein content, a moderate pleocytosis and markedly pathological colloid-tests. There was a pronounced microphthalmy in both eyes. There is iritis present on both sides. On an ophthalmoscopic examination being made,

there appeared to be grey-green masses projecting into the vitreous, presumably the result of an extensive destructive retinitis.

Attempts to isolate toxoplasmas by animal inoculation from the cerebrospinal fluid gave no results. It is possible that the cerebrospinal fluid was sterilized beforehand by the administration of large doses of sulfathiazole.

The toxoplasma neutralization test with the serum of the child was negative both with respect to the Bk.-strain and with respect to the SABIN-strain ; with the serum of the mother with regard to the SABIN-strain was negative, with respect to the Bk.-strain, positive.

CASE 19 [1]) : W. B., a girl, born in June 1946, is treated 2 months after birth for stunted growth.

FAMILY HISTORY : Both parents are healthy. The mother has never had a miscarriage. The patient is her first child. The syphilis tests in the blood of the parents are negative. The toxoplasma neutralization test with the serum of the mother is positive both with respect to the Bk.-strain and with regard to the SABIN-strain.

PERSONAL HISTORY : The girl was born at full-term and weighed 2.300 gr. at birth. The mother says that the child immediately after birth was cyanotic. There was secretion from the right ear for some days at the age of 6 weeks. There has been no contact with contagious diseases.

PHYSICAL EXAMINATION AND COURSE : The child weighed 3.250 grammes at the age of 2 months. It does not give the impression of being ill. The skin turgor and the muscle-tonus are normal. Chest and abdominal organs reveal no abnormalities. The reflexes are normal. After some days the fontanel appears to be somewhat taut. Meningeal symptoms, however, are not present. The circumference of the head is 38½ cm.

At the age of 6 months, the size of the head proves to have increased considerably and now amounts to 46 cm. The cranial sutures are wide. A physical examination brings to light a distinct spasticity of the muscles (Fig. 13). The reflexes are normal. In the later stages the child begins to vomit. It mostly has a bit of a temperature (up to 38.2 C.).

At the age of 7 months the child contracts acute otitis media accompanied by a considerable rise in temperature and meningeal symptoms. The cell-content of the cerebro-spinal fluid was then considerably enhanced. Paracentesis and the administration of penicillin and sulfadiazine soon restore the old condition. The size of the head continues to increase slightly.

RÖNTGENOGRAPHIC EXAMINATION OF THE SKULL : There is no calcification visible in the brain.

LABORATORY DATA : Examination of the Blood : The hemoglobin content amounts to 14 gm. Erythrocytes 4.980.000. Leukocytes 15.700 : eosinophils 1%, polymorphonuclear

[1]) BRÜCKNER c.s.

Fig. 13 : Case 19. Hydrocephalia. Spasticity of muscles.

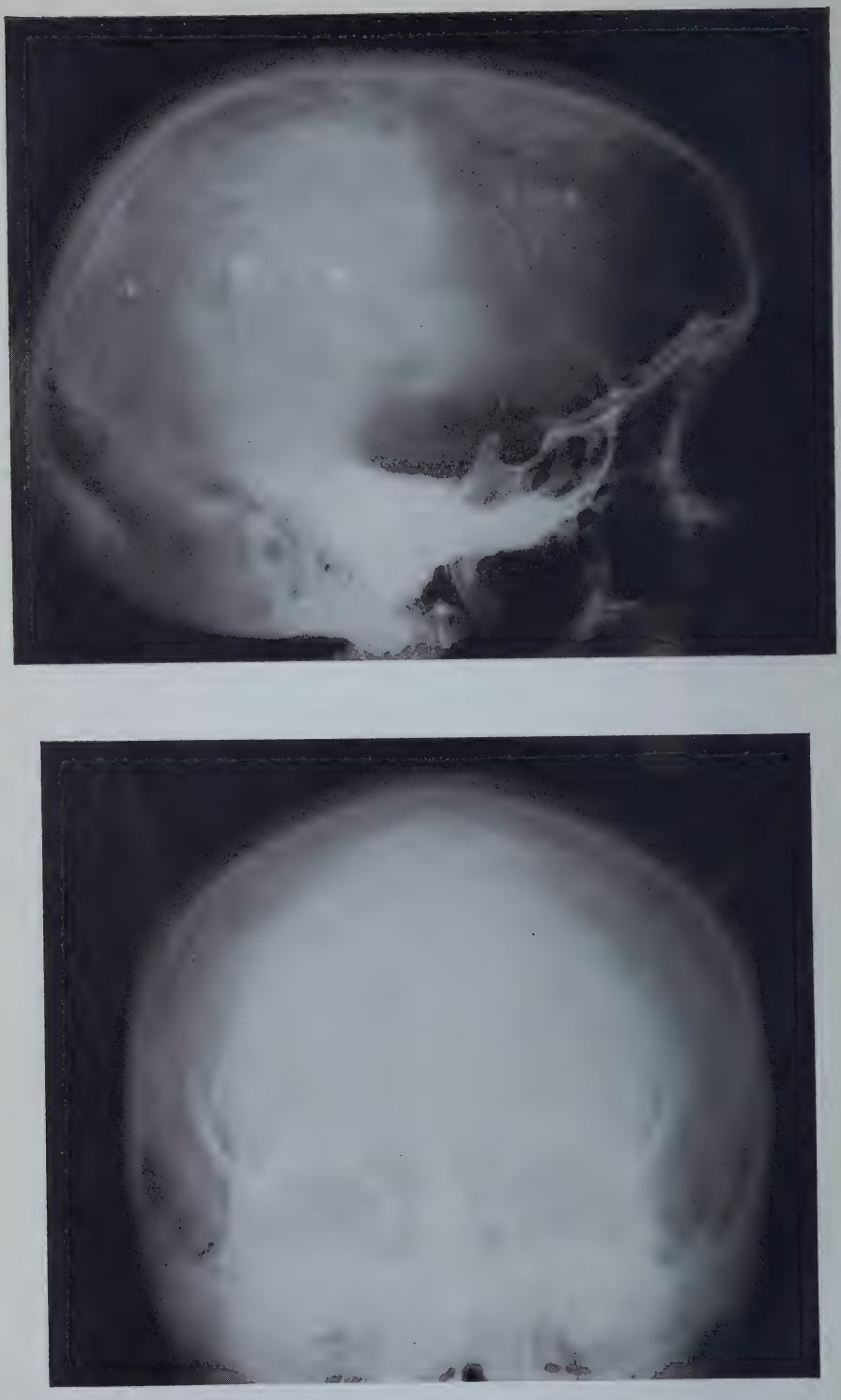

Fig. 14 : Case 20. Cerebral calcification.
Thickening of the bones of the skull.

leukocytes 16 %, lymphocytes 75 %, monocytes 8 %. The WASSERMANN and SACHS-GEORGI tests are negative. Examination of the Urine : no abnormalities.

Examination of the Cerebrospinal Fluid : The cerebrospinal fluid is clear and colourless. In the lumbar fluid the number of cells have risen in varying degrees (up to 75/3). The NONNE and the PANDY test are weakly positive. There is no pleocytosis in the ventricular fluid and the NONNE and the PANDY test are negative. The content of sugar amounts to 0.053 gr.%. No micro-organisms were found in the sediment of the cerebrospinal fluid on a direct examination. The WASSERMANN test is negative.

VENTRICULOGRAPHY : Pressure and cell content of the cerebrospinal fluid in the left and the right ventricle vary (pressure in the right ventricle 60 mm., in the left 45 mm.). Pressure is normal in the lumbar fluid. Phenol-red is injected into the right ventricle and is not recovered in the lumbar fluid. The right ventricle seems to be isolated from the rest of the ventricular system.

OPHTHALMOLOGIC EXAMINATION (January 1947) : There are laterally oscillating movements of the eyes. The eyes are directed downwards. One gets the impression that the perception of light is wanting. The eyes are about the normal size. The horizontal diameter of the cornea is 11 mm. on both sides. The anterior chamber bears a normal aspect.

The pupils are of equal size and round ; they fail to react to light. On the instillation of homatropine they dilate. There are no synechiae posteriores. The media are clear on both sides. Refraction is emmetropic on both sides.

Right fundus oculi : Throughout the whole fundus, but especially in the area around the papilla nervi optici there are focal chorioretinal atrophies of various sizes, shapes and intensity. The atrophy varies from complete atrophy of the retina and choroid to only atrophy of the pigmented epithelium. In and around these lesions there is pigmentation of varying intensity. The blood-vessels of the retina are very thin. The papilla nervi optici is oval in shape and chalk-white in colour. Between the focal lesions there is a slight shifting of pigment present throughout the fundus (Plate VI).

Left fundus oculi : There are similar changes as in the right fundus. Centrally there is a very large, completely atrophic lesion, manifesting an ectasy of roughly 4 diopters. The left papilla nervi optici, too, is chalk-white in colour (Plate VI).

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. 6 Mice and 4 guinea-pigs were intracerebrally injected with centrifugated cerebrospinal fluid when the child was 8 months old. In this and in consequent animal-passages no micro-organisms were found. It is possible that the energetical combined sulfadiazine and penicillin treatment preceding the tests have something to do with the sterility of the fluid.
B. Toxoplasma Neutralization Test : negative, both with respect to the Bk.-strain and with respect to the SABIN-strain.

SUMMARY : A girl of 2 months is admitted to hospital for observation on account of stunted growth. The size of the head increases rapidly. There is a spasticity of the muscles. The child has a temperature and vomits occasionally. In the cerebrospinal fluid there is a slight and varying increase of protein and of cells. The

right ventricle is isolated from the rest of the system. When the child was 7 months old it was found, during an ophthalmologic examination, that there was nystagmus and in both fundi an intensive focal, healed chorioretinitis together with extreme papillary-atrophy.

No toxoplasmas are encountered in the cerebrospinal fluid. Toxoplasma neutralization tests with the serum of the child were negative and with the serum of the mother, both with respect to the Bk.-strain and with regard to the SABIN-strain, they were positive.

CASE 20 : R. P., a man, born in 1920, was known to have chorioretinal lesions in both eyes since he was 5 years old. He was re-examined at the age of 27.

FAMILY HISTORY : There have been no special diseases nor abnormalities in the family. The patient is the youngest but one of a family of 5 children. Three brothers and one sister are all healthy. Two of the brothers have been ophthalmoscopically examined and have normal fundi. The mother used to be a healthy woman. She has had no miscarriages. At present she is suffering from a "rheumatic affection". She has normal fundi. The toxoplasma neutralization test with the serum of the mother is positive with respect to the Bk.-strain ; with respect to the SABIN-strain there was one negative and one positive result.

PERSONAL HISTORY : The birth had a normal course. During the first few years no symptoms were noted. At the age of 2 years he had a bad fit of convulsions, became cyanotic and lost consciousness. This was never repeated. During his childhood he has had German measles, measles and rickets. He has never had any lung-troubles. In his fifth year an ophthalmologist was consulted because it was found he was looking with one eye. It was then that a bilateral, old, chorioretinitis was discovered.

PHYSICAL EXAMINATION : The chest and abdominal organs show no abnormalities. PIRQUET's reaction is positive. On a neurologic examination being held no abnormalities were encountered. The reflexes are normal. Sensibility and co-ordination are undisturbed.

LABORATORY DATA : The blood-formula is normal. The sedimentation rate amounts to 4/8. The WASSERMANN test is negative. There are no abnormalities in the urine.

Examination of the Spinal Fluid : The lumbar punctate is under normal pressure and contains a normal percentage of protein and no cells. The benzoin and gold-sol tests are normal. The syphilis tests are negative.

RÖNTGENOLOGIC EXAMINATION : Röntgenoscopy of the chest-organs reveal no abnormalities. A röntgenographic examination of the skull revealed the presence of a number of foci of intense calcification in the brain-substance, and a moderate thickening of the tabula interna (Fig. 14).

OPHTHALMOLOGIC EXAMINATION : The patient looks exclusively with the right eye. The visual acuity on the right amounts to 1.5/20, with sph. — 6 = 4/10, and on the left 1.5/10, with sph. — 3 = 2/10. There is mild strabismus convergens and sursumvergens

of the left eye. The right eye is somewhat smaller than the left. The horizontal diameter of the cornea measures : right 11 mm. and left 12 mm. A slight enophthalmus of the right eye is attributed to microphthalmy. The media are clear on both sides.

Right fundus oculi : Inferonasally to the papilla there is a focal, post-inflammatory atrophy of the retina and choroid, three to four disc diameters in size. There is some pigmentation, for the most part at the edge. Superiorly to this lesion there are, on the nasal side of the papilla, two smaller, pigmented, old inflammatory lesions.

The papilla nervi optici, which is normal in colour, is surrounded by a dirty yellowish-grey zone, in which, on the temporal side, two cilio-retinal arteries arise (Plate VI).

Left fundus oculi : In the macular area there is a roughly round, intensely pigmented, old, inflammatory lesion, measuring three disc diameters in size. The papilla n. optici and the retinal blood-vessels are normal (Plate VI).

ATTEMPTS TO DIAGNOSE TOXOPLASMOSIS BY LABORATORY METHODS :

A. Intracerebral inoculation of mice and guinea-pigs with centrifugated cerebrospinal fluid and with the urine of the patient, caused no toxoplasmosis in the animals.
B. Serum Neutralization Tests : There is a negative result both with respect to the Bk.-strain and the SABIN-strain.

SUMMARY : Bilateral chorioretinal atrophic lesions are known to have been present since this patient was 5 years old. The history of the patient reveals one bad fit of convulsions at the age of 2 years. When he was 27, intensive calcifications were found in the brain and moderate thickening of the tabula interna of the bones of the skull. There was microphthalmy in the right eye.

The lesions, apparently, are the sequent of an abortive form of retino-encephalopathy in early life.

Confirmation of a probable toxoplasmic origin of the lesions in this apparently healthy man could not be obtained, since inoculation with the spinal fluid and with urine failed to produce toxoplasmic infection in animals and neutralization tests failed to reveal any definite anti-toxoplasmic activity of the serum of the patient, neither with respect to the Bk.-strain, nor with respect to the SABIN-strain of toxoplasma. The toxoplasma neutralization test with the serum of the mother was positive with regard to the Bk.-strain ; once negative and once positive with respect to the SABIN-strain of toxoplasma.

CHAPTER VII

DISCUSSION

I. DIAGNOSTIC PROCEDURES AND RESULTS

1. DIRECT EXAMINATION OF CEREBROSPINAL FLUID. ANIMAL INOCULATION. POST-MORTEM EXAMINATION

In 13 cases of retino-encephalopathy (cases 1 to 8 inclusive and 16 to 20 inclusive) the cerebrospinal fluid was examined for the presence of toxoplasma.

In cases 1 and 2 parasites resembling toxoplasma were found in stained smears of the sediment.

The finding of toxoplasma by direct examination of the cerebrospinal fluid is a fact that has rarely been described. The frequent paraventricular lesions are accounted for by the presence of parasites in the cerebrospinal fluid. These lesions in their turn cause spreading of the toxoplasma. If we are aware of this fact and if we are acquainted with the morphology of the parasites, toxoplasmas will certainly be found by direct examination of the cerebrospinal fluid more frequently.

In both cases it was possible to transmit the infection to laboratory-animals. The parasites isolated in this manner proved to be biologically and immunologically identical to toxoplasma. The toxoplasma-strain isolated in case 2 is referred to as the Bk.-strain and was often used in the toxoplasma neutralizing anti-body test. In cases 1 and 2 moreover toxoplasmas were encountered during the post-mortem examination in several inflammatory lesions in the brain and elsewhere, in case 1 also in one of the eyes.

The course of the animal-test in case 3 calls for a few remarks. In the brain of one of the two guinea-pigs inoculated with cerebrospinal fluid toxoplasma-like micro-organisms were encountered at the site of injection. In a subsequent intra-cerebral guinea-pig passage a few micro-organisms resembling toxoplasma were again met with in the brain. The question now arises as to whether the parasites were toxoplasmas and if they emanated from the spinal fluid. That it was not possible in subsequent passages to infect the animals fatally is contradictory to the increase in the virulence of the toxoplasma, which is usually observed in successive brain-passages. Of the behaviour of the toxoplasma in chronic cases, however, little is known. On the other

hand, we have to take into account the frequent occurrence of spontaneous protozoan infections in guinea-pigs, although in the guinea-pig strain used, no spontaneous protozoan infection had ever been noted.

The presence of parasites in the spinal fluid of the child, we do not, with the above in view, consider to be proved conclusively. We cannot, however, entirely reject the fact that it may be possible. Although the process seemed to be inactive clinically, yet from the appearance of fresh retinal lesions in the left eye, it was found that the inactivity in this case was only apparent (recurrent retinopathy). The animal inoculation took place during the presence of fresh retinal lesions in the left eye. The serum of the child and of the mother repeatedly showed a distinct toxoplasma neutralizing activity and for this reason we classified this case in the group of cases of retino-encephalopathy associated with positive serum neutralization test for toxoplasmosis.

In all the other cases both the direct microscopical examination of the cerebrospinal fluid and the animal inoculation test was negative. An examination of the blood (case 5) was likewise negative. It should be remembered in this connection that the examination in many cases was made a long time after the presumed onset of the infection, and moreover, in a few cases, it was made after the administration of large doses of chemo-therapeutics, which may have had an effect on the result [1]).

2. TOXOPLASMA NEUTRALIZING ANTI-BODY TEST (RABBIT-SKIN TEST)

Of 29 patients with active or inactive focal retinopathy, whether accompanied by cerebral symptoms or not, the blood-serum was examined for toxoplasma neutralizing anti-bodies. Of 27 mothers of patients and of one sibling (case 14) the blood-serum was also examined. The cerebrospinal fluid was examined in two cases, once of a patient and once of the mother of a patient [2]).

The rabbit-skin test is based on the comparison of the reactions to intra-cutaneous injection of antigen (mouse-brain infected with toxoplasma), whether mixed with test-serum or not.

Two different toxoplasma-strains were used as antigen. One of these strains (Bk.-strain of toxoplasma) was isolated from the cerebro-

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[1]) The animal inoculation experiments were carried out in the Laboratory of Parasitology (Head : Prof. Dr. P. H. VAN THIEL) and in the Institute of Preventive Medicine, Dept. of Bacteriology and Experimental Pathology (Head : Prof. Dr. J. D. VERLINDE), Leyden.

[2]) The neutralization tests were carried out in the Institute of Preventive Medicine, Dept. of Bacteriology and Experimental Pathology (Head : Prof. Dr. J. D. VERLINDE).

TABLE 3

Interpretation of Rabbit-skin Tests

		Final Dilution of Toxoplasma Suspension				Interpretation
		1 : 20	1 : 100	1 : 1000	1 : 10.000	
Rabbit X	mother A. Bk. (case 2)	++++	++	—	—	positive
14-10-47	control	++++	+++	++	—	
Bk.-strain	mother E. W. (case 3)	++++	+++	—	—	positive
Rabbit 216	A. B. (case 16)	++++	+	—	—	negative
28-10-47	B. L. (case 17)	++++	+++	—	—	negative
Bk.-strain	control	++++	++	—	—	
	mother Joh. S. (case 11)	++	++	—	—	doubtful
	Joh. S. (case 11)	+++	—	—	—	positive
Rabbit 204	R. P. (case 20)	+++	++	—	—	negative
7-11-47	mother R. P. (case 20)	++	+	—	—	negative
SABIN-strain	control	++	+	—	—	
	H. T. (case 14)	++	+	+	—	negative
Rabbit 202	A. de L. (case 18)	++++	+++	+++	+++	negative
7-11-47	mother A. de L. (case 18)	++++	+++	++	++	negative
SABIN-strain	control	++++	+++	+	—	
	W. B. (case 10)	++++	++	+	—	negative
	mother W. B. (case 10)	+++	+	+	—	doubtful
Rabbit 213	C. G.	++++	+++	++	—	negative
7-11-47	mother C. G.	++++	+++	+	—	negative
Bk.-strain	control	++++	+++	++	—	
	A. N. (case 8)	++	++	+	—	doubtful
	mother A. N. (case 8)	++++	++	+	—	doubtful
Rabbit 205	A. de L. (case 18)	++++	+++	+	—	negative
7-11-47	mother A. de L. (case 18)	++	+	—	—	positive
Bk.-strain	control	++++	+++	+	—	
	W. B. (case 19)	++++	++++	—	—	negative
	mother W. B. (case 19)	+++	+	—	—	doubtful
Rabbit 214	R. P. (case 20)	++	+	+	—	doubtful
7-11-47	mother R. P. (case 20)	++	+	—	—	positive
Bk.-strain	control	++++	+++	+	—	
	H. T. (case 14)					

10-11-47	H. W. (case 7)	++++	+++	+	—	positive
SABIN-strain	control	++++	+++	+++	+++	
	E. B. (case 5)	+++	++	+	—	positive
	cerebro-spinal fluid H. W. (case 7)	+++	++	+	+	doubtful
Rabbit 221	mother H. W. (case 7)	+	—	—	—	positive
10-11-47	H. W. (case 7)	++	—	—	—	positive
Bk.-strain	control	++	+	+	—	
	E. B. (case 5)	+	—	—	—	positive
	cerebro-spinal fluid H. W. (case 7)	++	—	—	—	positive
Rabbit 219	mother E. B. (case 5)	+	+	+	—	doubtful
12-11-47	control	++	++	+	—	
SABIN-strain						
Rabbit 233	mother E. W. (case 3)	++++	+++	+	—	doubtful
22-11-47	E. W. (case 3)	++++	++	—	—	positive
Bk.-strain	control	++++	++	++	+	
	E. W. (case 3)	+++	++	—	—	positive
Rabbit 211	mother A. v. D. (case 1)	+++	++	—	—	positive
8-12-47	mother A. v. D. (cerebro-spinal fluid)					
Bk.-strain	(case 1)	++++	++++	+++	+	negative
	control	++++	++++	+++	++	
Rabbit 203	control	++++	+++	+	—	
10-12-47	mother A. Bk. (case 2)	++	+	—	—	positive
Bk.-strain						
Rabbit 239	control	+++	+++	+++	—	
10-12-47	mother A. Bk. (case 2)	+	—	—	—	positive
SABIN-strain						
Rabbit 224	mother A. B. (case 16)	++++	+++	—	—	negative
30-12-47	control	++++	++	—	—	
Bk.-strain	mother B. L. (case 17)	++++	++	—	—	negative
Rabbit 207	mother H. M. (case 12)	++++	+	—	—	positive
5-1-48	H. M. (case 12)	++	+	—	—	positive
SABIN-strain	control	++++	+++	+	+	
Rabbit 306	J. v. d. B.	++++	++	—	—	doubtful
17-1-48	control	++++	++	+	—	
SABIN-strain	mother J. v. d. B.	+++	—	—	—	positive
Rabbit 306	J. v. d. B.	++++	++	—	—	doubtful
17-1-48	control	++++	++	+	—	
SABIN-strain	mother J. v. d. B.	+++	—	—	—	positive

TABLE 3 *(continued)*

Interpretation of Rabbit-skin Tests

		Final Dilution of Toxoplasma Suspension				Interpretation
		1 : 20	1 : 100	1 : 1000	1 : 10.000	
Rabbit 304	G. v. Br. (case 10)	++++	++	—	—	positive
17-1-48	mother J. V.	++++	+	—	—	positive
SABIN-strain	control	++++	+++	++	—	
	Mrs. v. Sch.-Br. (case 13)	++++	—	—	—	positive
	J. V.	++++	++	+	—	doubtful
Rabbit 307	mother M. Kl. (case 9)	+	—	—	—	positive
17-1-48	M. Kl. (case 9)	+	—	—	—	positive
SABIN-strain	control	++	++	—	—	
	mother Joh. Vl.	++	++	+	—	negative
	Joh. Vl.	++	++	++	—	negative
	I. T.	++	+	+	—	negative
		1 : 20	1 : 100	1 : 500	1 : 2500	
Rabbit 208	control	++++	++++	+	+	
12-2-48	G. de W.	++++	+++	+	+	negative
Bk.-strain						
Rabbit 243	E. B. (case 5)	+++	++	—	—	positive
19-2-48	mother E. B. (case 5)	++++	++	+	—	positive
SABIN-strain	control	++++	+++	+++	—	
	W. R.	++++	++++	+++	++	negative
	mother E. R.	++++	+++	+	—	doubtful
	mother G. de W.	++++	+++	+	—	doubtful
Rabbit 288	C. v. d. L. (case 4)	+	+	—	—	positive
4-3-48	control	++++	++	+	—	
Bk.-strain						
Rabbit 336	E. de W. (case 15)	++++	+++	+	+	negative
12-3-48	mother E. de W. (case 15)	++++	++	+	+	negative
SABIN-strain	control	++++	+++	+	+	
Rabbit 293	P. de C. (case 6)	+++	+	—	—	positive
19-3-48	mother P. de C. (case 6)	+	+	—	—	positive
SABIN-strain	B. L. (case 17)	+++	++	+	—	negative

19-3-48	H. T. (case 14)	++++	+++	+	+	negative
SABIN-strain	Ag. T. (case 14)	++++	+++	+	—	doubtful
	A. B. (case 16)	++++	+++	+	—	doubtful
	control	++++	++++	++	—	
Rabbit 296	J. V.	++++	++	++	++	negative
23-3-48	mother J. V.	++++	+	—	—	positive
Bk.-strain	control	++++	+++	++	+	
Rabbit 273	mother C. v. d. L. (case 4)	++	+	+	+	negative
23-3-48	control	++	+	+	—	
Bk.-strain						
Rabbit 270	L. v. d. B.	++++	+++	+	+	negative
2-4-48	mother L. v. d. B.	++++	+++	++	++	negative
SABIN-strain	Fr. R.	++++	+++	++	++	negative
	mother Fr. R.	++++	+++	++	—	negative
	Joh. K.	++++	+++	++	—	negative
	control	++++	+++	++	+	
Rabbit 382	N. B.	++++	++	—	—	negative
2-4-48	mother N. B.	+++	++	—	—	negative
SABIN-strain	control	+++	+	—	—	
Rabbit 280	mother W. B. (case 19)	++++	+	—	—	positive
8-4-48	W. B. (case 19)	++++	++	+	+	negative
Bk.-strain	control	++++	+++	+	+	
Rabbit 268	A. N. (case 8)	+++	+	+	—	positive
8-4-48	mother A. N. (case 8)	+++	+	—	—	positive
Bk.-strain	R. P. (case 20)	++++	++	+	+	negative
	mother R. P. (case 20)	++++	+	—	—	positive
	mother A. v. D. (case 1)	++++	+	—	—	positive
	control	++++	+++	++	+	
Rabbit 289	mother A. N. (case 8)	++	+	—	—	positive
8-4-48	R. P. (case 20)	++	++	+	+	negative
SABIN-strain	mother R. P. (case 20)	++	+	—	—	positive
	mother A. v. D. (case 1)	++	+	—	—	positive
	control	+++	++	+	+	
Rabbit 284	mother W. B. (case 19)	+++	++	—	—	positive
8-4-48	W. B. (case 19)	++++	+++	++	++	negative
SABIN-strain	control	++++	+++	++	++	

spinal fluid of an infant (case 2), while the other strain was provided by Dr. SABIN (SABIN-strain of toxoplasma). It turned out that the two strains, if not identical, are very closely related to each other.

The rabbit-skin tests were carried out according to SABIN's technique (see Chapter II). It was found desirable, however, to introduce a few slight modifications. A final dilution of toxoplasma suspension 1 : 10.000 seldom caused a skin-lesion in the control-test. In later tests, therefore, 1 : 20, 1 : 100, 1 : 500 and 1 : 2500 dilutions were used. SABIN traced the outline of the skin-lesions on transparent paper. Not only is the border of the lesion often difficult to define, but it seemed to us to be more exact to evaluate also the extension of the lesion in depth.

The relative intensity of the lesions on the eighth day was finally indicated as ++++, +++, ++, + and —. The evaluation of the lesions was based on: 1. surface extension of the lesion (papular swelling, erythema); 2. extension in depth (palpable infiltrate); 3. presence and extension of central necrosis.

Before proceeding to the interpretation of the tests, we procured an idea as to the variety of the rabbit-skin lesions after injecting the same quantity of antigen. From this it appeared that in the lower concentrations there may be a difference of one "skin-lesion unit".

We interpreted the tests as follows (Table 3). [1])

Negative results with serum kept longer than 24 hours after the removal of the blood are not mentioned. In several cases a positive result could be reproduced with serum taken at another time, or with serum preserved in a frozen or dried state.

From the interpretation of the tests it appears that only a *positive* test (presence of toxoplasma neutralizing anti-bodies) could be determined upon if there was an inhibition of the skin-lesions, which clearly exceeded the limits of the variety-range of the lesions. If the inhibition of the lesions exceeded the limits of the variety-range but slightly, we termed the test *doubtful*, by which we indicate that no verdict was possible. In these cases the test was repeated if possible.

The criterion set by us for a positive test is more severe than that imposed by most authors. Moreover there is one factor, which has not been taken into account. The reactions to antigen-inactive serum-mixtures are often more pronounced than those to antigen-Tyrode-mixtures. SABIN also refers to this. By leaving this unspecific influence of the serum out of consideration, we increased in many a test the evidence of the neutralizing activity of the material examined.

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[1]) Where it is not otherwise mentioned, the material examined consisted of bloodserum.

The test result in two cases calls for further explanation. The serum of mother R. P. (case 20) was twice positive with respect to the Bk.-strain, whereas with regard to the SABIN-strain it was once positive, but on another occasion was negative. The serum of mother A. DE L. (case 18) turned out to be positive with respect to the Bk.-strain and negative to the SABIN-strain. We are at a loss to account for this. We have designated the result of the tests in both cases as doubtful.

We give the final results of all the neutralizing tests with blood-serum and cerebrospinal fluid in patients, mothers of patients and siblings in Table 4.

TABLE 4

Final Evaluation of Test Results

	Patients				mothers of patients		siblings
	name	age	blood-serum	cerebro-spinal fluid	blood-serum	cerebro-spinal fluid	blood-serum
1	A. v. D. (case 1)	2½ months			positive	negative	
2	A. Bk. (case 2)	3 months			positive		
3	E. W. (case 3)	8 years	positive		positive		
4	C. v. d. L. (case 4)	2 years	positive		negative		
5	E. B. (case 5)	17 months	positive		positive		
6	P. de C. (case 6)	2½ years	positive		positive		
7	H. W. (case 7)	14 months	positive	positive	positive		
8	A. N. (case 8)	15 months	positive		positive		
9	M. Kl. (case 9)	10 years	positive		positive		
10	G. v. Br. (case 10)	13 years	positive				
11	J. S. (case 11)	7 years	poritive		doubtful		
12	H. M. (case 12)	19 years	positive		positive		
13	Mrs v. Sch.-Br. (case 13)	54 years	positive				
14	H. T. (case 14)	15 years	negative		negative		doubtful
15	E. de W. (case 15)	10 years	negative		negative		
16	A. B. (case 16)	17 years	negative		negative		
17	B. L. (case 17)	14 years	negative		negative		
18	A. de L. (case 18)	1 year	negative		doubtful		
19	W. B. (case 19)	2 years	negative		positive		
20	R. P. (case 20)	27 years	negative		doubtful		
21	C. G.	4 years	negative		negative		
22	J. v. d. B.	21 years	doubtful		positive		
23	J. V.	13 years	negative		positive		
24	Joh. Vl.	6 years	negative		negative		
25	I. T.	30 years	negative				
26	G. de W.	11 years	negative		doubtful		
27	W. R.	7 years	negative		doubtful		
28	L. v. d. B.	12 years	negative		negative		
29	Fr. R.	16 years	negative		negative		
30	Joh. K.	24 years	negative				
31	N. B.	17 years	negative		negative		
	patients tested : 29				mothers of patients tested : 27		siblings tested : 1

The serum of 29 patients was examined. In the case of 11 patients the neutralizing test was positive, in 17 patients negative, while in one case the result was doubtful. Among the 11 positive patients there were 10 with presumably congenital retinopathy and 1 with acquired retinopathy (Table 5).

TABLE 5

Retinopathy Associated with Positive Serum Neutralization Test for Toxoplasmosis (April 1948)

	author	number of cases	age at examination
Probable congenital retinopathy	Wolf, Cowen and Paige (6); Koch c.s.	6	8 months—11 years
	Sabin (4)	?	0—15 years
	Vail, Strong and Stephenson	5	7—23 years
	Crothers	7	?—12 years
	Wagener	1	infant
	Heath and Zuelzer	1	2 months
	Schwarz and Wendell	2	5 years
	Heidelman	17	1 month— 25 years
	Adams	1	14 months
	Adams c.s.	1	14 years
	Johnson c.s.	4	3—5 years
	Miller	1	infant
	Author	10	10 months—19 years
Acquired retinopathy	Vail, Strong and Stephenson	1	?
	Heidelman	8	20—52 years
	Rucker	1	51 years
	Johnson c.s.	16	15—50 years
	Author	1	53 years

Furthermore we examined the serum of 27 mothers of patients. With 12 of the mothers the neutralization test was positive, with 10 of the mothers negative, while it was not possible to come to any

decision about 5 of them; it was not possible either to evaluate the serum of the twin-sister of a patient (case 14).

The neutralization test with the cerebrospinal fluid of the mother in case 1 was negative, with that of the patient in case 7 positive.

The patients 1 to 20 inclusive form the subject of a full description in the preceding chapter [1]).

II. AGE AT COMMENCEMENT OF SYMPTOMS; PRENATAL OR POSTNATAL INFECTION; SOURCE OF INFECTION

In 19 of the 20 cases there are indications of the infection arising very early in life, in many a case prenatally.

Prenatal infection undoubtedly took place in case 7, since directly after birth grey pupils were noted in both eyes and in case 8, in which immediately after birth it was remarked among other things that the eyes were abnormally small. In both cases the toxoplasma neutralization test with the serum of the mother is positive.

In the other cases the first symptoms were observed at ages ranging from a few days to 8 years. In many of these cases there was reason to assume that there, too, the infection was prenatal.

The serum of 8 mothers has a distinct toxoplasma neutralizing activity. In the case of 3 mothers the result of the neutralization test was doubtful, of 5 mothers negative, while in the case of one mother the test was not made. Microphthalmy might point to an infection of the eye prior to birth, nl., in case the eye is smaller than the normal eye would have been at birth. This applies exclusively only if the microphthalmy rests on a stunted growth of the eye and a secondary shrinkage of the eye is not involved. The pronounced microphthalmy

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[1]) During control-tests, Dr. WINSSER (2) made a significant observation nl. that the intensity of the reactions of the rabbit-skin to the same quantity of antigen diminishes in caudal direction. An attempt was made to make the comparison of the serum lesions with the control lesions more accurate by means of statistical considerations. As a criterion for a positive test a 95 % significant difference with the control-lesions was taken. As to the patients described in Chapter VI, it follows from this that the presence of toxoplasma neutralizing anti-bodies should not be assumed in 11, but in 14 patients (case 11 to be interpreted as negative, cases 14, 15, 16 and 20 as positive), and that the sera of 12 mothers were positive, of 11 mothers were negative and of 4 mothers were doubtful (mothers case 3 and 8 to be interpreted as negative, mothers case 14 and 20 as positive).

It is now quite out of the question to allow for this new point of view in the classification of the cases described.

in cases 1, 5, 7, 8 and 18 form a strong indication of prenatal infection of the eye.

We have already referred to the possibility of a prenatal infection being activated during or after birth. Hence it is not ruled out entirely that in case 3 the vaccination has had some effect on the course of the illness.

In one case (case 13) the development of retinopathy at a more advanced age is an established fact. We discovered the retinal lesion by chance in a very early stage in a 53-year-old woman, in other respects healthy. Whereas infantile ocular toxoplasmosis is a subject of frequent comment in literature, adult ocular toxoplasmosis is less often described. VAIL c.s., HEIDELMAN and JOHNSON c.s. report on 1, 8 and 16 cases of acquired chorioretinitis in an active or inactive stage respectively. There were no other abnormalities in any of the cases.

Concerning the source of infection in our patients and their mothers, we are not in a position to supply any positive data. It is, however, worth mentioning that in case 13, shortly before the outbreak of retinopathy a „very sick" cat had been in the house. The cause of the animal's disease, however, is unknown.

III. CEREBRAL SYMPTOMS [1])

The cerebral symptoms revealed by 16 patients (cases 1 to 9 and 14 to 20 inclusive) are caused by focal inflammatory and degenerative lesions of the brain.

The cause of the cerebral symptoms was not to be recognized in all cases at the onset of the disease. In case 3, the cause of the neurological disturbances (slabbering, speech defect) and of the disturbed mental development was for a long time unknown. In case 6 a congenital malformation of the brain was assumed to be the cause at first of the symptoms (backwardness, convulsions). In the cases 4 and 14, the encephalitic nature of the disease (backwardness, convulsions) was not comprehended in the beginning either. In all these cases the discovery of inflammatory fundus lesions led to the assumption of a post- or chronic-encephalitic state. From this the diagnostic significance of the retinopathy in the retino-encephalopathic syndrome becomes evident.

The course of the encephalopathy varied. In the cases 15 and 20 the affection of the central nervous system continued to be

[1]) For a full description of the cerebral symptoms in cases 1, 5 and 7, we refer the reader to the complete publication of these cases.

latent till intracerebral calcifications were noted on the X-ray photo of the skull (Fig. 12, 14). The physical and mental development of the two patients had been quite normal! In the cases 4 and 9 only once had convulsions been observed during infancy. In other cases again cerebral symptoms dominated at an early stage (hydrocephalia, convulsions, backwardness, neurological disturbances, abnormalities of the cerebrospinal fluid) and were sometimes progressive in the subsequent course of the disease (progressive hydrocephalia).

Hydrocephalia was the most striking symptom (Fig. 3, 9, 10, 13). It was present in 8 cases of retino-encephalopathy (cases 1, 2, 4, 5, 6, 7, 8 and 19). In cases 3, 14 and 16 there was mild microcephalus. In case 9 there were pathological impressiones digitatae in the bones of the skull. In case 20 the bones of the skull were strikingly thickened (Fig. 14).

Intra-cerebral calcifications were present in 10 cases (case 1, 2, 3, 4, 5, 7, 8, 15, 16 and 20) (Fig. 7, 10, 12, 14). The appearence of these calcifications is indicative of healed or healing necrotizing cerebral lesions. The various shapes of the calcium shadows demonstrated by röntgenography may be accounted for by the size of the lesions. Peripheral calcification of large necrotic lesions, as are frequently present in the basal ganglia and thalami, is probably the cause of the curvi-linear appearance of the calcium shadows (Fig. 10), while multiple, irregular calcium deposits may appear in smaller lesions in the cerebral hemispheres.

It would seem that only infection occasions calcification in the brain at a very youthful age. JOHNSON c.s. have reviewed all the cases of toxoplasmic "chorioretinitis" occurring in the literature on the subject and concluded that cerebral calcification in patients who had toxoplasmosis with chorioretinitis was observed only when the age at the commencement was known to be not over 15 years. Our own observations agree with this.

Although calcifications in the brain are not visible röntgenologically in all cases of toxoplasmic encephalopathy (see also cases 6 and 9) "the röntgenographic demonstration of intra-cerebral calcifications is one of the outstanding clinical features of toxoplasmic encephalitis" (WOLF, COWEN and PAIGE (6)). DYKE c.s. mention intracerebral calcifications in 8 of the 9 cases of toxoplasmic encephalitis observed by them.

One occasionally finds the view wrongly defended in the literature on the subject, that intracerebral calcifications are pathognomonic in toxoplasmic encephalitis. Calcium deposits in necrotic lesions is more

likely to be an unspecific process, which can also be observed in traumatic lesions or in inflammatory lesions of another etiology (tuberculosis).

Convulsions were noted in 9 cases. Neurological disturbances of a very divergent character (defective speech, slabbering, weakness, spasticity, tremor, abnormal reflexes, labile body-temperature, hemiplegia, incontinentia) were present in several cases.

In 13 patients the mental development was moderately to seriously disturbed. In cases 9, 15 and 20, however, mental development was found to be quite normal.

Cerebrospinal fluid : Changes in the cerebrospinal fluid were found in 8 patients, while in 1 patient the cerebrospinal fluid was not examined, and in the rest of the patients the fluid at the time of examination showed no abnormalities. In the cases 1, 2, 7 and 18 were indeed the most typical changes : a very high protein content, very slight if any increase of cells (albumino-cytologic dissociation), xanthochromia and pathological colloidal tests. These changes are considered to be characteristic of toxoplasmic encephalitis in an early stage. Ulceration of the ventricular surface of the brain is probably reponsible for many of the changes that occur.

Ventriculography was applied to 6 patients (cases 1, 2, 5, 7, 8 and 19). In all six cases an internal hydrocephalus was found to be present with considerably dilated and often displaced lateral ventricles. On introducing air into the ventricles there arose in cases 1 and 8 the so-called "honeycomb-pattern" of the ventricles (Fig. 3, 10). Dyke c.s. who also saw this in two cases, put this phenomenon down to the presence of gas-bubbles in the ventricles caused by a very high protein content of the ventricular fluid.

The „honeycomb-pattern" of the ventricles does not probably only occur in toxoplasmic encephalitis.

For the rest we mention splenomegalia (cases 3 and 13), hepatomegalia (case 13), increased erythrocyte sedimentation rate (cases 12 and 13), mild or moderate eosinophilia in the peripheral blood (cases 2, 4 and 7) and a weakly positive melanin test in the urine (case 13).

IV. OCULAR MANIFESTATIONS

1. CLINICAL SIGNS :

Ocular symptoms occupy a significant place in the syndrome. In 7 of 16 cases in which besides ocular symptoms, cerebral symptoms are also present, yet it was an abnormality of one or both

of the eyes (microphthalmy, enophthalmy, grey pupil, poor vision, squint, nystagmoid movements of the eyes etc.), which was noted first and in a very early stage (from immediately post partum to 2 months after it)! Where there were no cerebral symptoms, bad vision (sometimes first noted at school-going age), strabismus or nystagmus was the reason to examine the eyes. In case 13 the affection was discovered by chance.

Retinopathy: Focal fundus lesions are present in all the patients. They were first observed at ages varying from 5 weeks to 53 years. In 4 cases (cases 10 to 13 inclusive) retinopathy is the only manifestation, in the other cases there are cerebral symptoms besides (retino-encephalopathy).

We have already touched upon the significance of inflammatory fundus lesions in determining the nature of a cerebral disease, particularly with a view to post-encephalopathic sequelae.

KOCH c.s. referred to the significance of „chorioretinitis" in diagnosing infantile toxoplasmosis. Their conclusion in reference to the cases examined clinically and histo-pathologically by them was that „it would appear that toxoplasmic chorioretinitis occurs in most, if not in all instances of infantile toxoplasmic encephalomyelitis and is of diagnostic aid in the clinical recognition of this disease".

To some extent we share KOCH and his colleagues' opinion. During our investigations with respect to the occurrence of toxoplasmic infection, we were guided by the presence of focal fundus lesions and in this way were able to compile a fairly large number of cases of retinopathy and retino-encephalopathy of proved or presumably toxoplasmic etiology.

On the other hand it is certain that the absence of ophthalmoscopically visible, focal fundus lesions do not preclude infantile toxoplasmosis. In several cases of infantile toxoplasmosis no mention is made of ocular abnormalities in the literature concerned. The eyes were not examined in all cases. In a single case the fundus oculi was found to be normal (DE LANGE). In FREUDENBERG's case, the fundus oculi was at first normal, fundus lesions arising only later on (BRÜCKNER).

Special significance is attached to case 2 in this respect. This is the only case known in which a negative ophthalmoscopic examination was histologically confirmed.

Opinions concerning this question as to whether the fundus lesions in toxoplasmosis have a characteristic appearance or not, vary with different authors. JOHNSON c.s. consider the recognition of toxoplasmic "choroiditis" with the ophthalmoscope not very feasible. VAIL c.s.,

too, are of opinion that the appearance of toxoplasmic chorioretinitis is not characteristic. KOCH c.s. are the only ones who express themselves more positively. After studying the ocular symptoms in all the cases of infantile toxoplasmosis observed by them up till 1943 (WOLF and COWEN (1); WOLF, COWEN and PAIGE (1, 5); KOCH c.s.) they come to the conclusion that „ophthalmoscopically the intraocular lesions of toxoplasmic encephalomyelitis have certain characteristics that seem to distinguish them clearly and would appear to render them diagnostic: 1. occurrence of severe and extensive focal chorioretinal lesions in infants and in children; 2. regularity of bilateral involvement of the macular region; 3. tendency to bilateral occurrence of other lesions; 4. tendency to involvement of the periphery in one or more quadrants of the retina and choroid; 5. punched-out appearance of large and small lesions in the late phase; 6. occurrence of massive chorioretinal degeneration, extensive connective tissue proliferation and heavy pigmentation, as contrasted with the dissociation of these changes in other chorioretinal lesions; 7. presence of an essentially normal retina and vasculature surrounding the lesions in all stages of the infection; 8. tendency to the occurrence of associated congenital defects in the eyes; 9. rapid development of sequential optic nerve atrophy, and 10. constant clarity of the media in the presence of severe chorioretinitis".

In 5 of the 20 cases observed by us the retinopathy was unilateral (cases 2, 6, 9, 12 and 13), whereas in the other 14 cases the affection was bilateral (Plate I to VI inclusive).

The lesions occurred everywhere in the fundus, both centrally and in the extreme periphery. They were both very small and very extensive. In some cases pretty well the whole retina seemed to be involved The number of lesions present in one eye, too, varied considerably. In a few eyes there was one single large or small lesion, whereas in other eyes there were multiple lesions, sometimes as smaller satellite lesions of one large macular lesion, sometimes spread over the whole fundus oculi.

In 5 cases we saw fresh fundus lesions (cases 3, 5, 7, 13 and 18). In case 3 we observed fresh lesions in one of the eyes in the macular region next to inactive changes, years after the presumable commencement of the disease. There were 7 very small, miliary, grey foci in the retina, which after a few months were completely resorbed (Plate II). The presence of these fresh retinal lesions point to the chronic-recurrent character of the infection, which, clinically, seemed to be completely inactive. In the cases 5, 7 and 18 there are extensive, fresh retinal changes in both eyes (Plate II, III). In case 13 we could trace the uni-

lateral retinal lesion from a very early stage and could observe the very slow and gradual change into a chronic lesion, which even two years after thecommencement still clearly showed some activity (Plate IV)!

Fresh fundus lesions are greyish-yellow-white coloured, fairly well-defined, sometimes greatly swollen areas in the retina, of varying sizes and shapes. While in case 3 there were very small later totally resorbed lesions, in cases 5, 7, 13 and 18 had changed large portions of the retina. In cases 5 and 7 there was a fair amount of sub-retinal fluid. In case 13 there were retinal hemorrhages surrounding the lesion. KOCH c.s., VAIL c.s. and BRÜCKNER, too, have mentioned the occurrence of hemorrhages round the lesions.

The appearance of the fresh toxoplasmic fundus lesions bear the characteristics of a necrotizing retinopathy. The larger lesions show a resemblance to the artificial coagulation of the retina.

In all other cases there were even at the first ophthalmoscopic examination inactive lesions. There were no more changes in the fundus picture in the subsequent course of the disease. The inactive lesions are sharply outlined, varying in size and shape, and characterized by an atrophy of the underlying choroid of varying intensity, even total atrophy of the choroid. In a few cases there is an ectasy of the sclera. Practically all the lesions are slightly or considerably pigmented whether at the border or scattered over the whole surface. In several lesions there is a bluish-grey, tumorlike mass, mostly intensively pigmented at the border, round or oval in shape, which is presumably the result of the organization of inflammatory masses (cases 4, 8, 9, 10, 13, 14 and 16). (Plate II, III, IV, V).

Since a useful description of the fundus lesions cannot be done very satisfactorily, we have given as far as possible coloured drawings, which do more justice to the ophthalmoscopical aspect of the retinopathy.

Atrophy of the Optic Nerve Head: In 20 eyes there was a pallor of the papilla. In 3 eyes the papilla was atrophic without there being any focal fundus lesions present (case 2 and case 6). Atrophy of the optic nerve has often been observed in infantile toxoplasmosis.

Irido-cyclitis: In several cases of infantile toxoplasmosis in the literature on the subject mention is made of iritis (WOLF, COWEN and PAIGE (5); ZUELZER and HEATH; HEIDELMAN; GASSER and SCHWARZ; BRÜCKNER), but little or no attention has been paid to its nature and its significance. KOCH c.s. in their article on the "Significance of Ocular Lesions in the Diagnosis of Infantile or Congenital Toxoplasmosis" do not even make any mention of this symptom.

We witnessed iritis in 5 cases (cases 1, 5, 7, 8 and 18) of more or less active toxoplasmic retinopathy. The iritis has a diffuse character. Hyperemia of the iris, haziness of the iris-pattern and the presence of adhesions to the anterior capsule of the lens betray the state of things. In case 7 (left eye) there was a distinct "iris bombans". Iritis is presumably due to the toxic influence of the retinal process (Fig. 4, 8, 11).

In case 13 the presence of fine precipitates against the cornea and of particles suspended in the anterior chamber betrayed a mild cyclitis.

We are of the opinion that the existance of iritis has a certain diagnostic value. A right evaluation of the iritis in the case described by GASSER and SCHWARZ as fetal rubeola or toxoplasmosis, certainly turns the scale in favour of toxoplasmosis.

In case 1 we found remnants of a pupillary membrane. WOLF, COWEN, PAIGE, and HEATH and ZUELZER likewise describe this phenomenon.

HEATH and ZUELZER observed inflammatory changes in the pupillary membrane (fetal iritis).

Cataract: In case 7 there was a partial cataract (Fig. 8). We have not noted opacities of the lens in any of the other cases. Cataract is but seldom mentioned in the literature concerned. KOCH c.s. witnessed a posterior cortical cataract, while in the case of GASSER and SCHWARZ both lenses were wholly cataractous.

It is of importance to know that cataract may occur in infantile toxoplasmosis, as otherwise confusion might arise with the sequelae of fetal rubeola-infection.

Microphthalmus: A slight to high degree of microphthalmia was noted by us in 11 of the 19 cases of infantile retinopathy (cases 1, 3, 4, 5, 6, 7, 8, 11, 14, 18 and 20), unilateral (cases 3, 4, 6, 14 and 20) or bilateral (cases 1, 5, 7, 8, 11 and 18). Microphthalmus is frequently mentioned in the literature on infantile toxoplasmosis. In JANKÛ's case there is a unilateral microphthalmus. Further reports on the occurrence of microphthalmus have been made by WOLF, COWEN and PAIGE; HEATH and ZUELZER; HEIDELMAN; BAMATTER; GASSER and SCHWARZ. This symptom has turned out to be one of importance in infantile toxoplasmosis. The pathogenesis and significance of the microphthalmus in connection with the time of the infection of the eye we have discussed elsewhere.

Strabismus, nystagmoid movements and *deviation of the eyes* are frequent symptoms in infantile toxoplasmic retino-encephalopathy.

We have often met with *refractive errors* in children with congenital retinopathy, mostly myopia and astigmatism, which have also been observed by KOCH c.s.

2. HISTO-PATHOLOGICAL EXAMINATION OF THE EYES

In the cases 1 and 2 ophthalmological examination was made prior to death, whereas histo-pathological examination of the eyes took place in both cases after death. We are adding the histological description of the eyes in both cases of infantile toxoplasmosis to those reports of histological examinations of the eyes in 9 cases appearing in the literature on the subject (Table 6).

TABLE 6

Toxoplasmic Retinopathy. Histopathologic Examination of the Eyes (April 1948)

	author	case	age at death	number of eyes examined	number of eyes with retinal lesions	number of eyes in which toxoplasmas are found
1	JANKÛ	—	11 months	2	2	1
2	WOLF and COWEN (1)	J. S.	30 days	2	2	2
3	WOLF, COWEN and PAIGE (1)	C. D.	31 days	1	1	1
4	WOLF, COWEN and PAIGE (5)	B. R.	birth	2	2	not mentioned
5	WOLF, COWEN and PAIGE (5)	L. M.	9 weeks	2	2	2
6	HEATH and ZUELZER	H.	1 month	1	1	1
7	BAMATTER (3)	—	27 days	2	2	2
8	KEAN and GROCOTT	—	1 day	?	?	?
9	GASSER and SCHWARZ	—	11 months	2	2	?
10	Author	A. v. D.	2½ months	2	2	1
11	Author	A. Bk.	3 months	2	1	0

Retina: In case 1 a focal retinal lesion was found in one of the eyes at the age of 5 weeks. The ophthalmoscopical examination was made very difficult by the haziness of the media. The lesion made the impression of a slightly active retinopathy (Plate I).

At the histological examination a chronic-proliferous retinitis

was found to be present in both eyes, with the formation of a partly still young granulation-tissue, rich in blood-vessels and infiltrated with plasma cells and lymphocytes. The pigmented epithelium is partly destroyed, partly proliferated. The choroid is pretty well unchanged! In one of the eyes we saw toxoplasma-colonies in the granulation-tissue. Evidently these toxoplasmas have lost their virulence ("burned-out case of toxoplasmosis") (Fig. 5).

The inflammation is mainly localized peripherally, extending from the ora serrata in a backward direction. Ophthalmoscopically a paracentral off-shoot of the peripheric retinal lesion was observed in one of the eyes.

In case 2 only few retinal changes were seen with the ophthalmoscope. A slightly changed colour of the retina and a waving of the retinal vessels were interpreted as a possible flat detachment of the retina, a few light and dark spots having been observed lying in the extreme periphery.

During the microscopic examination we encountered several folds of the retina of various sizes and here and there a little sub-retinal fluid. There is some doubt about the significance of this as there is a chance of post-mortem changes, seeing that the eyes were only removed 36 hours after death. No distinct anatomical substratum was found for the above-mentioned peripheric light and dark spots.

In one single place a peri-vascular inflammatory lesion in the retina was encountered (Fig. 6). Toxoplasmas were not found in it. This case, too, therefore, should be included in the group of retino-encephalopathies.

Nervus Opticus: In both cases there is an atrophia nervi optici, which, in case 2 was even visible ophthalmoscopically. In case 2 there is an infiltration of the optic nerve sheaths present (perineuritis optica).

Perineuritis optica and interstitial neuritis optica was also observed by KOCH c.s., BAMATTER, etc.

Uvea: In the uveal tract there are slight inflammatory changes in both cases. Whereas the latter in case 2 are restricted to a sub-clinical and only microscopically perceptible inflammation of the ciliary body and of the iris, in case 1 there is a diffuse, macroscopically visible iritis (hyperemia of the iris, synechiae posteriores, haziness of the anterior chamber of the eye and of the iris). The blood-vessels are dilated throughout the uveal tract. There are in the choroid, mainly under the retinal lesion, a few small lymphocytic infiltrations.

3. REMARKS ON THE PATHOGENESIS OF OCULAR SIGNS IN TOXOPLASMOSIS

It is generally admitted that the infection of the various organs with toxoplasma takes place via the blood-stream. JANKÛ compared

the mode of infection to that in congenital syphilis. WOLF and COWEN (1) pointed out the susceptibility of the brain and of the eyes to toxoplasmic infection. As to the infection of the eye they considered 3 possibilities : 1. Infection of the eye as well as the brain by way of the blood-stream. 2. Infection of the eye by way of the sub-arachnoid space in the optic nerve sheaths to the ocular bulbs after the brain has been infected. They point out in this connection the inflammatory reaction observed by themselves in the optic nerve sheaths. 3. Infection of the brain secondary to the infection of the eye.

Afterwards KOCH c.s. deemed it most likely that the infection of the eye is effected via the blood-stream.

HEATH and ZUELZER, too, speak of a "special susceptibility of the central nervous system", the toxoplasma demonstrating a "destructive affinity for young nerve tissue, especially that of the eye". They assume that there is a preference of the infection for the macular region and explain this by pointing out that the nerve-tissue of the macular region differentiates last (after the eight month).

WOLF and COWEN (1) observed that the presence of the parasite in the tissues produced an inflammatory and productive reaction, which was associated with necrosis where the process was severest. They held a toxic product of the parasites responsible for the necrosis, the inflammatory and productive reaction being considered secondary to the necrosis.

ZUELZER saw the intensity of the lesions changing with the number of parasites. He saw in principle the same process everywhere nl. an acute vasculitis followed by foci of necrosis and cellular infiltration or by productive granulomatous changes. In the vicinity of necrotic lesions he invariably found many parasites. He looks upon granulomatous lesions as a response to a small number of parasites. He saw granulomatous lesions only in the central nervous system.

Different writers fail to give a clear pronouncement on the pathogenesis of the fundus lesions. It is as KOCH c.s. remark : "until the earliest stages of the chorioretinal infection are available for pathological study, the initial site of infection of the eye cannot be stated with certainty". JANKÛ's opinion is that in his case the choroid in the macular region was the chief site of the inflammatory process, the retinal changes and the destruction of the pigmented epithelium being reactions on the choroiditis. JOHNSON c.s. speak of "choroiditis". By far the greater number of writers speak of "chorioretinitis" (KOCH c.s., HEATH and ZUELZER, BAMATTER, KEAN and GROCOTT, etc.).

HEATH and ZUELZER are the only ones who say that "inflammatory

foci were mostly retinal and gave the impression that this layer was the point of origin". We are also of the opinion that in ocular toxoplasmosis the primary localization of the process takes place in the retina.

The retino-tropism of the toxoplasma expresses itself in the pretty well exclusive occurrence of the toxoplasma in the retina (JANKÛ; WOLF and COWEN (1); WOLF, COWEN and PAIGE (1); HEATH and ZUELZER; BAMATTER; HEPDING). Only WOLF and COWEN (1) mention once, next to the presence in abundance of toxoplasma in a retinal lesion, the presence of parasites in a choroidal exudate, directly under the retinal lesion. Toxoplasmas have not been described elsewhere in the eye. In case 1 we, too, found the toxoplasma-colonies exclusively in the retina (Fig. 5).

Most histopathological descriptions, moreover, mention the fact that the retina is the seat of highly destructive and, as a rule, necrotic changes, while in the choroid the changes are restricted to a mild non-specific inflammation, mainly in the choriocapillary layer under the retinal lesion. An analogous relation exists between the lesions in the brain and in the meninges: in the vicinity of extensive necrotic lesions in the nerve-tissue only a mild inflammatory reaction of the leptomeninges is mostly encountered.

In conclusion we mention an observation made by us in experimental infection of rabbits-eyes with toxoplasma. When we introduced the toxoplasma into the anterior chamber, a necrosis and an inflammatory-reaction in the iris and to a lesser degree in the ciliary body resulted. In a few sections the process was found to have extended in a backward direction. The anterior part of the retina showed a disintegration of the architecture, an incipient necrosis, while a large number of parasites were met with in the retina. The underlying choroid was normal! From this, too, the retino-tropism of the toxoplasma was evident.

The focal, chronic-proliferous lesion in case 1 is a very fine example of a process being almost entirely localized within the retina, the underlying choroid revealing few or no inflammatory changes. The pigmented epithelium has nowhere completely disappeared. (Fig. 5).

The intra-ocular inflammatory signs in case 2 are restricted to a peri-vasculitis in the retina. This granulomatous lesion of the retina is to be regarded as an initial toxoplasmic lesion and forms an argument, not only for the primary retinal localization, but also for the hematogenous origin of the retinopathy (Fig. 6).

Hence we think we are right in regarding the fundus lesions in toxoplasmosis as a consequence of retinopathy.

The inflammatory signs in the choroid and in the anterior portion of the uveal tract must be looked upon as a toxic reaction. They are most pronounced in extensive retinal necrosis. Toxoplasmic iritis is a diffuse toxic iritis (Fig. 4, 8, 11).

Opacification of the lens in toxoplasmosis is of the so-called cataracta complicata type (Fig. 8).

KOCH c.s. ascribe the optic atrophy to various factors : destruction of the retina, inflammation of the optic nerve itself and intracranial processes. Peri-neuritis and neuritis optica presumably play a significant role in causing optic atrophy. The pronounced optic atrophy in case 2 is, we suppose, very closely associated with the perineuritic cellular infiltration met with. It is not to be determined with any degree of certainty if this peri-neuritis is of a specific toxoplasmic or of a toxic nature. We failed to find any toxoplasmas in case 2 either in the optic nerve itself or in the optic nerve sheaths.

Minor malformations of the eyes have been described several times in ocular toxoplasmosis. JANKÛ attributed the malformation of the left eye in his case to a probable action of toxic products, arising from the parasites, upon the eye during development. He also thought of the possibility of a trophic influence of the abnormal hydrocephalic brain on the development of the eye. WOLF, COWEN and PAIGE (1) also account for such-like malformations by the infection of the eye during development. They conclude that the infection in their cases has occurred at a late stage in fetal life, since major malformations of the eye were absent.

As to whether there is any connection between the presence of membrana pupillaris persistens (case 1) and retinal folds (case 2) on the one hand and toxoplasmic infection on the other, we will not enter into here. We will, however, not ignore the frequent occurrence of microphthalmy in infantile toxoplasmosis. According to KOCH c.s. it would seem likely that the presence of the infection of the eye during intrauterine life interferes with its normal development. HEATH and ZUELZER, too, consider microphthalmy a consequence of the inflammation : "a small eye may result from uveitis whether principally anterior or posterior".

With JANKÛ, KOCH c.s. and HEATH and ZUELZER we think that the infection of the eye plays a great part by its effect on the development of the eye. In several cases we saw a relation between the severity of the intra-ocular inflammatory process and the degree of microphthalmy. Yet we wish to refer to another factor which may have effect on the size of the eye, nl. a shrinkage of the eye (atrophia bulbi).

Some signs in the microscopic preparations of case 1 might be indicative of an incipient atrophia bulbi (Fig. 5). The pars plana of the ciliary body and the anterior portion of the choroid have become detached from the underlying sclera, the choroid has three times its normal thickness everywhere mainly through a considerable dilatation of the blood-vessels, the optic nerve head projecting into the vitreous. When drawing conclusions as to the time of infection from the size of the eye, we ought to take into consideration the possibility of shrinkage of the eye.

V. FAMILY EXAMINATIONS

The presence of toxoplasma in members of one family is not mentioned in the literature on the subject. BAMATTER found toxoplasmas during a histological examination of one of the children of a twin that died of congenital encephalitis, but he fails to mention a similar discovery in the other child that died of ulcerative enterocolitis.

WOLF, COWEN and PAIGE (4, 6), SABIN (4), VAIL c.s., CROTHERS, HEATH and ZUELZER, HEIDELMAN, JOHNSON c.s., ADAMS and others report on toxoplasma neutralizing anti-bodies in the blood of mothers and siblings in cases of congenital toxoplasmic infection. HEIDELMAN found toxoplasma neutralizing anti-bodies in the blood of one of two fathers of suchlike children examined by him. In two families JOHNSON c.s. found toxoplasma neutralizing anti-bodies in the blood of the other children, in one of the families even in 7 of the 9 children. ADAMS found a positive neutralization test in 8 siblings! One of the twin-children described by ZUELZER and HEATH had toxoplasma neutralizing anti-bodies in the serum, while in the other child toxoplasmas were found at autopsy.

Symptoms have rarely been noted in the mothers and siblings which might be caused by toxoplasmic infection. The pregnancies resulting in infected children were not always perfectly normal. Spontaneous delivery before term occurred several times. Also praematurе rupture of the membranes has occurred. In Vos's case the mother was found to be suffering, some years after the birth of her toxoplasmic child, from diabetes insipidus, which was put down to a chronic encephalitis. CROTHERS and JOHNSON c.s. report on the occurrence of intracerebral calcifications in mothers of congenitally infected children. HEIDELMAN described chorioretinitis in a mother of a child with congenital chorioretinitis, which we also saw on one occasion (case 11). In addition to the observations of infected twins,

(ZUELZER and HEATH ; BAMATTER) symptoms have also been described in siblings. Hence CROTHERS noted in one family chorioretinitis, intracerebral calcifications and convulsions in 2 of the children, in a third child intracerebral calcifications only ! On the other hand JOHNSON c.s. found no clinical symptoms of infection nor toxoplasma neutralizing anti-bodies in the serum of the children of 2 mothers with toxoplasmic choroiditis.

As already mentioned we found toxoplasma neutralizing anti-bodies in the serum of 12 mothers of children presumed to be infected prenatally.

There are some abnormalities in a few mothers. In case 11, presumably congenital retinopathy, child of a mother with acquired retinopathy, we have at our disposal a similar observation as that made by HEIDELMAN. The mother had severe papillo-chorioretinitis and cyclitis shortly before pregnancy. It is very likely that there is some connection between the eye-affection of the mother and the retinopathy of the child.

In case 3 the mother has been suffering from persistant headaches since the birth of the child. Six years after the birth of the child she was found to have a pronounced hyperostosis of the frontal bones of the skull. We will not discuss whether this hyperostosis stands in any relation to an otherwise latent toxoplasmic infection, but just mention the fact. The mother in case 14 and the patient in case 20 also have strikingly thick skull-bones. DYKE c.s. and GLANZMANN (1), too, make mention of a thickening of the bones of the skull. SABIN (4) found toxoplasma neutralizing anti-bodies in the serum of "5 individuals, 10 to 69 years of age with unexplained encephalopathies presenting predominantly severe persistant headaches, in some associated with hyperostosis frontalis interna".

In case 7, the mother is said to have had "poliomyelitis" in her youth, on account of which she now still limps.

The interpretation of diseases of the mother during pregnancy is no easy matter either. We know that in adults toxoplasmic infection may be accompanied by fever and exanthema (PINKERTON and HENDERSON) (see the mother in case 4).

Finally we will mention the symptoms we observed in the other children of the same mother. It is known that 3 mothers gave birth to still-born children after the infected child (cases 6, 9 and 10), in case 10 even on three successive occasions ! This surely recommends the examination of still-born children. In case 11 the patient, when 3 years old, had a sister who suffered from recurrent retrobulbar neuritis, the cause of which could not be found. Afterwards

complete recovery was effected. The twin sister of the patient in case 14 has some calcium shadows in the brain! In case 15 we would refer to the neurological disturbances shown by 2 of the other children (paresis of the musculus peronaeus, HORNER's syndrome). In case 7 the first child of the mother died when it was 6 weeks old of "desiccation".

The frequency of symptoms in some families is too striking to be put down to chance.

SUMMARY

Protozoa resembling toxoplasma were first observed in animals by LAVERAN (1900). Such-like protozoa received the name of toxoplasma from NICOLLE and MANCEAUX (1909). The animal kingdom is presumably the source of human infection. The mode of infection in man is still a matter of hypothesis.

In 1923 JANKÛ gave us the first description of a case of human disease caused by toxoplasma-like protozoa; he described the ocular manifestations in detail. Since 1939 it has become an established fact that similar cases may be caused by toxoplasma (WOLF, COWEN and PAIGE).

The diagnosis of toxoplasmosis is made by demonstrating the toxoplasma in body-fluids or in tissues secured by autopsy or biopsy, whether by direct microscopical examination or by animal inoculation. Toxoplasmas have now been encountered in various organs in more than 49 cases. In some cases the toxoplasma has been isolated by animal inoculation.

The presence of specific anti-bodies in the blood-serum is of great diagnostic value.

Experimentally some sulfonamides have been found to be therapeutically effective in the acute stage of the infection. Presumably it is not possible to sterilize toxoplasma-carriers with sulfonamides.

The clinical picture of toxoplasmosis is variable. The infection may be clinically latent (carrier toxoplasmosis). It is possible for a mother with clinically inapparent toxoplasmosis to give birth to a child with manifest toxoplasmosis. In many cases, especially in infants, the toxoplasma shows an affinity for the central nervous system. Ocular manifestations are often met with in cases of toxoplasmic myelo-encephalopathy, but may be the only manifestation of toxoplasmosis.

Altogether 31 patients have been examined. In two cases (cases 1 and 2) the diagnosis had been established by the presence of toxoplasmas in the cerebrospinal fluid and was confirmed at autopsy by

the presence of toxoplasmas in the tissues, in case 1 in one eye, too. The remaining cases were selected on the ground of ocular abnormalities resembling those in toxoplasmosis, whether accompanied by cerebral disorders or not. The cerebrospinal fluid was examined in another 11 patients for toxoplasmas. In case 3 toxoplasma-like parasites were encountered in laboratory animals inoculated with spinal fluid; the course of the inoculation tests however furnished no proof that these toxoplasmas originated in the spinal fluid of the patient.

In 11 of 29 patients examined toxoplasma neutralizing anti-bodies were found in the blood-serum (cases 3 to 13 inclusive), also in 12 of 27 mothers of patients. The "rabbit-skin test" requires a few modifications. It is desirable to make the series of inoculations in the cranio-caudalward direction (WINSSER). Further it is to be recommended to use inactivated serum in the control-test and to carry out tests in duplicate.

In conclusion we described 7 patients with ocular signs and cerebral symptoms resembling those seen in toxoplasmosis (cases 14 to 20 inclusive).

We witnessed the appearance of ocular manifestations at adult age in case 13, in all the other cases we are concerned with symptoms present at a youthful age, in a few cases certainly, in others presumably the consequence of prenatal infection.

In toxoplasmosis of the brain, the spinal-cord and the retina we used the terms toxoplasmic myelo-encephalopathy and toxoplasmic retinopathy. To our minds injury to the retina stands in the foreground in toxoplasmosis of the eye.

The encephalopathy, which we have described in 16 cases, gave rise to very varied symptoms. In 2 cases it was fatal (cases 1 and 2), in one single case it was quite latent (case 15), whereas in other cases the disease was abortive (cases 9 and 20) or gave rise to hydrocephaly, microcephaly, convulsions, backwardness, neurological disturbances, pathologic cerebrospinal fluid. Intracerebral calcifications were present in 10 cases.

The ocular manifestations have been described clinically in all cases, in two cases also histo-pathologically (cases 1 and 2). In the last-mentioned cases there was in the main a retinal localization of the process. In case 1 there was a bilateral, chronic-necrotizing retinopathy with toxoplasmas in one of the eyes; the choroid was almost quite normal. In case 2 there was one small retinal granuloma (initial retinopathy); no toxoplasmas were found in this. In all other cases focal fundus lesions were observed. The question is discussed as to

whether the ophthalmoscopic picture is characteristic of toxoplasmosis. It is likely that neither the occurrence of lesions in one or in both eyes, nor the localization of the lesions in the fundus, nor the size and the number of lesions are pathognomonic. Only the fresh necrotic toxoplasmic retinal lesion may have a pathognomonic aspect (appearance of coagulated retina). Fresh retinopathy was seen in five cases. Inactive fundus lesions are probably not to be distinguished from chorioretinal atrophy by other causes.

Optic atrophy was present in 20 eyes, in 3 eyes without focal fundus lesions. In 5 cases there was iritis visible even macroscopically. Toxoplasmic iritis is of significance from a diagnostic point of view. It is a diffuse, adhesive iritis, presumably of toxic origin.

In one case (case 7) a cataracta complicata was present.

Eleven cases revealed a microphthalmy, unilateral or bilateral. In drawing conclusions about the time of the infection from the size of the eye, one has to be cautious as shrinkage of the eye may take place (atrophia bulbi). In addition, we frequently encountered strabismus, nystagmus, deviatio bulbi, refractive errors (myopia).

For a clinical diagnosis of toxoplasmosis an ophthalmoscopical examination is indispensable, because :

1. Toxoplasmic retinopathy may be the only manifestation of toxoplasmosis and an ophthalmoscopical examination may lead to the recognition of toxoplasmic infection (mono-symptomatic ocular toxoplasmosis).

2. The presence of toxoplasmic retinopathy may lead to the discovery of toxoplasmic lesions of the central nervous system.

3. The presence of fundus lesions resembling those in toxoplasmosis may be an indication of the toxoplasmic nature of a cerebral disease. The absence of ophthalmoscopically visible fundus lesions, however, do not preclude the possibility of toxoplasmosis.

We were able to confirm this latter by histo-pathological examination of the eyes in a case of infantile toxoplasma-encephalitis.

Finally reference was made to the frequency of symptoms in the families of patients, which seems to point to familial infection. In our own material the following have been met with in the mothers of patients : papillo-retinitis, hyperostosis frontalis, paresis of the leg, still-born children, and in siblings : retro-bulbar neuritis, intracerebral calcification, peronaeus-paralysis and HORNER's syndrome.

RESUME

En 1900 LAVERAN a observé pour la première fois des protozoaires qu'on a reconnus plus tard comme des toxoplasmes. Le nom de toxoplasme leur a été donné en 1909 par NICOLLE et MANCEAUX.

C'est probablement dans le règne animal qu'il faut chercher la source de la contamination de l'homme. Sur le mécanisme de la contamination chez l'homme il n'existe que des hypothèses.

JANKÛ a donné en 1923 la première description d'un cas d'infection humaine dûe à des protozoaires ressemblants au toxoplasme ; ce sont surtout les manifestations oculaires qu'il a décrites. En 1939 il a été prouvé irréfutablement que des cas pareils peuvent être causés par le toxoplasme (WOLF, COWEN et PAIGE).

La toxoplasmose se diagnostique par la présence du toxoplasme dans le liquide céphalo-rachidien ou dans les organes. Cette présence est établie soit par l'examen microscopique soit par l'inoculation chez l'animal. A présent le toxoplasme chez l'homme a été décrit dans plus de 49 cas. Dans quelques cas on a réussi à isoler le toxoplasme par une inoculation chez l'animal. L'activité anti-toxoplasmique du sérum a elle-aussi sa valeur diagnostique.

Plusieurs sulphonamides se sont montrées efficaces dans l'infection aigüe expérimentale. Il est probablement impossible de stériliser les cas chroniques de porteurs de toxoplasmes par des sulphonamides.

La symptomatologie de la toxoplasmose est variée. Il existe des formes inapparentes (porteurs de toxoplasmes). On a vu des femmes atteintes d'une forme inapparente mettre au monde des enfants atteints d'une toxoplasmose manifeste. En plusieurs cas surtout chez les nourrissons et les jeunes enfants, le toxoplasme affecte le système nerveux central. Les localisations oculaires sont dans ces cas-ci très nombreuses, ce qui n'implique pas que les dites localisations oculaires ne se montrent pas sans symptômes cérébraux.

L'auteur a examiné 31 malades au total. Dans les deux premiers cas les examens laboratoires avaient révélé la présence de toxoplasmes dans le liquide céphalo-rachidien ; après la mort on trouvait aussi des toxoplasmes dans les organes et dans le premier cas également

dans l'oeil droit. Les autres cas ont été sélectionnés quant aux lésions oculaires ressemblantes aux lésions oculaires toxoplasmiques, accompagnées ou non de symptômes cérébraux. Le liquide céphalo-rachidien de onze autres malades a été également examiné, dont le résultat était négatif à l'exception du cas no. 3, où l'on rencontrait des protozoaires ressemblants au toxoplasmes dans le cerveau des animaux inoculés avec le liquide de la malade. Il n'est d'ailleurs pas irréfutable que les toxoplasmes dans ce cas-ci ne provinssent du liquide.

Chez 11 des 29 malades on était à même de démontrer la présence d'anti-corps neutralisants dans le sérum (les cas no. 3—13 inclus) ; ce qui était également le cas chez 12 des 27 mères des malades.

On pourrait améliorer la technique du „rabbit-skin test" de SABIN par de légères modifications p.e. en injectant les dilutions de toxoplasme dans la direction du crâne à la queue (WINSSER). Il serait en outre recommandable d'employer du sérum inactivé pour faire le contrôle et de faire le test en double.

L'auteur a décrit finalement 7 cas de malades montrant les symptômes oculaires et cerébraux de la toxoplasmose (cas no. 14—20 inclus).

Dans le cas no. 13, les symptômes se présentaient chez une adulte ; dans tous les autres cas il était question de jeunes malades ; dans quelques cas les symptômes étaient sans aucun doute d'origine prénatale.

En indiquant la toxoplasmose du système nerveux et du fond de l'oeil, l'auteur s'est permis de parler de myelo-encéphalopathie et de rétinopathie toxoplasmiques. Selon son opinion les lésions toxoplasmiques du fond de l'oeil sont essentiellement des lésions de la rétine.

Dans les 16 cas d'encéphalopathie cités existait une grande diversité de symptômes.

Dans deux cas la maladie fut mortelle (cas no. 1 et 2), dans un seul cas elle restait latente (cas no. 15). Quelques fois le progrès en était abortif (cas no. 9 et 20), tandis que dans plusieurs cas elle donnait lieu soit à une hydrocéphalie ou une microcéphalie, soit à des convulsions, à une arriération mentale, à des désordres neurologiques et à un liquide céphalo-rachidien pathologique. La radiographie mettait en évidence des calcifications cérébrales dans 10 cas.

Les symptômes oculaires ont été dans tous les cas observés dans la clinique, dans deux cas également histopathologiquement (cas no. 1 et 2). Dans les 2 derniers cas il s'agissait surtout d'une lésion rétinienne. Dans le 1r cas (no. 1) il y avait une rétinopathie chronique nécrotisante dans tous les deux yeux tandis que la choroïde était à peu près normale.

Dans l'oeil droit on constatait des toxoplasmes dans la rétine. Dans le 2d cas (no. 2) il existait un petit granulome rétinien (rétinopathie initiale), dans lequel aucune trace de toxoplasmes. Dans le reste des cas on observait à l'aide de l'ophtalmoscope des foyers rétiniens.

La question s'impose s'il y a un aspect pour les foyers rétiniens qui soit caractéristique pour la toxoplasmose. Il est probable que ni la localisation des foyers, ni la grandeur et le nombre des lésions est pathognomique. Il n'y a que les fraîches lésions nécrotisantes toxoplasmiques qui puissent avoir un aspect pathognomique, qui alors ressemblent à des coagulations artificielles de la rétine. Des lésions fraîches ont été observées dans 5 cas. Selon toute probabilité les lésions inactives toxoplasmiques du fond de l'oeil ne diffèrent pas des lésions atrophiques dûes à d'autres causes.

Une atrophie du nerf optique était présente dans 20 yeux ; dans 3 yeux non-accompagnée de lésions rétiniennes.

Dans 5 cas on rencontrait une irite qui était déjà visible à l'oeil nu. L'irite toxoplasmique est d'une assez grande valeur pour le diagnostic. C'est une irite diffuse et adhésive, probablement d'origine toxique.

Dans un seul cas (no. 7) l'auteur peut signaler une cataracte compliquée. Dans onze cas il y avait une microphtalmie soit unilatérale soit bilatérale. La grandeur de l'oeil peut être indicative pour le moment de l'infection à moins qu'il ne s'agisse d'une atrophie.

En dernier lieu nous avons rencontré fréquemment : des strabismes, des nystagmes, des déviations conjuguées, des anomalies de la réfraction (myopie).

L'examen du fond de l'oeil est indispensable pour le diagnostic de la toxoplasmose, parce que :

1. une rétinopathie toxoplasmique peut être la seule manifestation de la toxoplasmose et que l'examen du fond de l'oeil peut aboutir à la découverte d'une infection toxoplasmique qui sans cela serait restée latente.
2. la présence d'une rétinopathie toxoplasmique peut mener à la découverte d'une toxoplasmose jusque là inapparente du système nerveux central.
3. dans le cas d'une affection du système nerveux central, la présence de lésions du fond de l'oeil ressemblantes à celles de la toxoplasmose peut être d'une valeur significative pour le diagnostic, bien que l'absence de lésions oculaires n'exclut pas la possibilité d'une toxoplasmose du système nerveux central.
   Un examen histopathologique des yeux dans un cas d'encéphalite toxoplasmique chez un nourrisson a confirmé ce fait.

Finalement l'auteur attire l'attention sur la fréquence des anomalies présentes dans les familles des malades souffrants de la toxoplasmose, ce qui pourrait indiquer une infection familiale.

Chez les mères des malades cités ci-dessus nous avons rencontré : une papillo-rétinite, une hyperostose frontale, une parésie d'une jambe et des enfants morts-nés, tandis que chez les autres enfants de ces familles nous avons pu observer : une neurite rétrobulbaire, des calcifications cérébrales, une paralysie du péronier, et un syndrôme de HORNER.

ZUSAMMENFASSUNG

Toxoplasmaähnliche Protozoen wurden im Tierreich entdeckt von LAVERAN (1900). NICOLLE und MANCEAUX nannten sie Toxoplasma (1909). Der Mensch wird wahrscheinlich vom Tier infiziert. Der Infektionsmodus des Menschen ist aber noch unsicher.

JANKÛ (1923) teilte den ersten Fall einer von toxoplasmaähnlichen Protozoen verursachten Krankheit beim Menschen mit und zwar beschrieb er hauptsächlich den Augenbefund. 1939 stellten WOLF, COWEN und PAIGE einwandfrei fest, dasz das Toxoplasma der Erreger ähnlicher Krankheitsbilder sein kann.

Zur Diagnose der Toxoplasmose dient die Demonstration des Toxoplasmas in Körperflüssigkeiten und im Gewebe, bei der Obduktion oder während des Lebens, entweder direkt mikroskopisch oder im Tierversuch. In über 49 Fällen sind jetzt Toxoplasmen im Gewebe beschrieben. In einigen Fällen wurden Toxoplasmen im Tierversuch isoliert. Die Anwesenheit spezifischer Antikörper im Blutserum stützt die Diagnose in erheblichem Masze.

Es stellte sich im Tierversuch heraus, dasz die Sulfapräparate das akute Stadium der Toxoplasmosis günstig beeinflussen können. Es ist wahrscheinlich nicht möglich Toxoplasmatrager mit Sulfapräparaten zu sterilisieren.

Das klinische Bild der Toxoplasmosis ist wechselnd. Die Infektion kann latent bleiben (Toxoplasmaträger). Eine latent infizierte Mutter kann ein manifest toxoplasmatisches Kind bekommen. In vielen Fällen, namentlich in der infantilen Periode, hat das Toxoplasma eine Affinität für das zentrale Nervengewebe und stehen nervöse Symptome im Vordergrund. Augentoxoplasmose findet man in Fällen mit nervöser Lokalisation in hohem Prozentsatz, aber auch als einziges Symptom einer Toxoplasmainfektion.

31 Patienten wurden untersucht, während 20 Patienten ausführlich beschrieben wurden. In den Fällen 1 und 2 war die Aetiologie der Krankheit bekannt, weil Toxoplasmen in der Zerebrospinalflüssigkeit

gefunden wurden. In beiden Fällen wurde die Diagnose bei der Obduktion bestätigt. Im ersten Fall wurden auch in einem Auge Toxoplasmen angetroffen. Die anderen Fälle zeigten alle Augensymptome wie sie bei der Toxoplasmose vorkommen können, eventuell von zerebralen Symptomen begleitet. Die Zerebrospinalflüssigkeit wurde bei weiteren 11 Patienten auf Toxoplasmen untersucht. Im dritten Fall wurden toxoplasmaähnliche Protozoen gefunden im Gehirn zweier Versuchstiere in zwei Passagen. Dieser Befund bot jedoch keine Sicherheit, dasz die Protozoen aus der Zerebrospinalflüssigkeit des Kranken stammten.

11 von 29 Patienten hatten Toxoplasma neutralizierende Antikörper im Blutserum (Fälle 3 bis 13 einschl.), und auch 12 von 27 Müttern. Der sogenannte „rabbit-skin test" nach SABIN bedarf einiger kleinen Modifikationen. Es ist erwünscht, die Injektionsreihe in craniocaudaler Richtung zu machen (WINSSER). Empfehlenswert ist es vielleicht inaktiviertes Serum als Kontrollflüssigkeit anzuwenden und die Untersuchungen immer in Duplo vorzunehmen.

Weiter beschrieben wir 7 Patienten mit toxoplasmosisähnlichen Augensymptomen und zerebralen Störungen (Fälle 14 bis 20 einschl.).

Im Falle 13 erstand die Augenaffektion im späteren Leben, in allen andern Fällen fanden die Symptome ihren Ursprung sehr früh im Leben, in einigen Fällen sicher, in anderen Fällen wahrscheinlich pränatal.

Bei Toxoplasmosis des Gehirns und des Rückenmarks und bei Toxoplasmosis der Netzhaut redeten wir von toxoplasmatischer Myelo-enzephalopathie respektiv von toxoplasmatischer Retinopathie. Unserer Meinung nach steht bei einer Lokalisation des Toxoplasmas im Auge die Netzhautschädigung im Vordergrund.

Die verschiedenartigen Symptome einer Enzephalopathie beschrieben wir in 16 Fällen. In den Fällen 1 und 2 war die Enzephalopathie tödlich, ein einziges Mal war sie ganz latent (Fall 15), in anderen Fällen war der Verlauf abortiv (Fälle 9 und 20) oder führte zu schweren Folgeerscheinungen (Hydrozephalie, Mikrozephalie, Konvulsionen, Imbezillität, neurologische Störungen, pathologischer Liquor-Befund). Kalkablagerung im Gehirn fanden wir in 10 Fällen.

Der Augenbefund wurde in allen Fällen klinisch beschrieben, in zwei Fällen (Fälle 1 und 2) auch histo-pathologisch. In diesen letzten Fällen bestand eine vorwiegend retinale Lokalisation des Prozesses; im ersten Fall eine doppelseitige chronisch-proliferative Retinopathie mit Toxoplasmen in einem Auge während die Chorioidea fast ganz normal war, und im zweiten Fall bestand ein einziges kleines Netzhaut-

granulom (initiale Retinopathie), in dem keine Toxoplasmen nachzuweisen waren. In allen andern Fällen wurden ophthalmoskopisch Veränderungen festgestellt. Es wird die Frage besprochen in welchem Masze das ophthalmoskopische Bild der Toxoplasmose charakteristisch ist. Es ist wahrscheinlich dasz weder das ein- oder doppelseitige Vorkommen der Augenherde, weder die Lokalisation der Herde im Augenhintergrund, noch die Grösze und die Zahl der Herde pathognomonisch sind. Nur der frische nekrotische toxoplasmatische Retinopathie dürfte einen typischen Aspekt haben, wie der Aspekt einer artefiziellen Koagulationsnekrose der Netzhaut. Eine frische Retinopathie bestand in 5 Fällen.

Inaktive Augenhintergrundsherde sind wahrscheinlich nicht zu unterscheiden von Atrophien anderer entzündlicher Aetiologie.

Eine Optikusatrophie bestand in 20 Augen, von denen in 3 Augen ohne Retinopathie. In 5 Fällen bestand eine schon makroskopisch sichtbare Iritis. Die toxoplasmatische Iritis hat diagnostischen Wert. Es ist eine diffuse, adhaesive Iritis, wahrscheinlich toxischer Art. Eine Katarakta complicata war im Falle 7 anwesend.

11 Fälle zeigten eine ein- oder beidseitige Mikrophthalmie. Die Grösze des Auges gibt keinen Aufschlusz über den Zeitpunkt der Infektion in Fällen sekundärer Schrumpfung des Auges (Atrophia bulbi). Strabismus, Nystagmus, Deviatio bulbi, Refraktionsanomalien (Myopie) wurden vielfach angetroffen.

Die Augenspiegeluntersuchung ist für die Diagnose der Toxoplasmose wichtig, weil:

1. Eine Retinopathie das einzige Symptom einer Toxoplasmose sein kann und die ophthalmoskopische Untersuchung zur Erkennung einer sonst latent gebliebenen toxoplasmatischen Infektion führen kann (monosymptomatische Augentoxoplasmose).
2. Die Feststellung einer toxoplasmatischen Retinopathie zur Aufdeckung toxoplasmatischer Herde im zentralen Nervensystem führen kann.
3. Toxoplasmosisähnliche Augenhintergrundsherde gewisse zerebrale Erscheinungen als Folge einer Toxoplasmosis identifizieren können. Es musz aber betont werden dasz ein negativer ophthalmoskopischer Befund die Möglichkeit einer Toxoplasmosis nicht ausschlieszt. Wir könnten das bestätigen durch eine histologische Augenuntersuchung in einem Falle von infantiler Toxoplasma-Enzephalitis.

Zum Schlusz erörterten wir die auffallend hohe Frequenz von Symptomen bei Familienmitgliedern unserer Patienten, was eine

familiäre Infektion suggeriert. Bei den Müttern wurden angetroffen: Papilloretinitis, Hyperostosis frontalis, Lähmung eines Beines und verschiedene Totgeburten, während bei den Geschwistern eine retrobulbäre Neuritis, intrazerebrale Kalkablagerungen, eine Peronaeuslähmung und ein HORNER Syndrom gefunden wurden.

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Case 1. Left eye

Plate II Retinopathy Associated with Positive Serum Neutralization Test for Toxoplasmosis

Case 3

Right eye Left eye

Case 4

Right eye Left eye

Case 5. Right eye Case 6. Right eye

Plate III Retinopathy Associated with Positive Serum Neutralization Test for Toxoplasmosis

Case 8

Right eye Left eye

Case 7. Right eye Case 9. Right eye

Case 10

Right eye Left eye

Plate IV Retinopathy Associated with Positive Serum Neutralization Test for Toxoplasmosis

Case 11

Right eye

Left eye

Case 12. Left eye

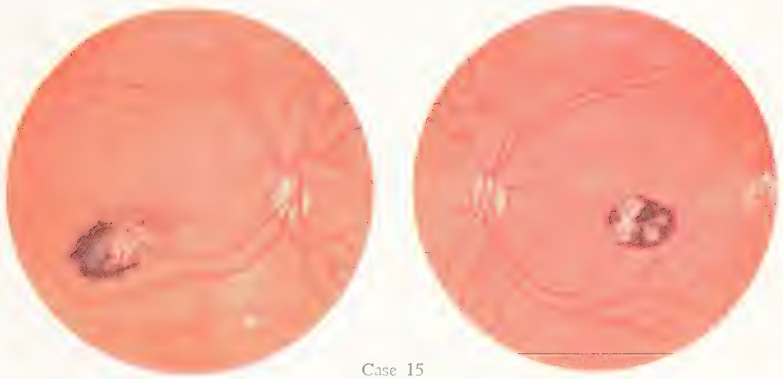
Case 13

Left eye (May 1946)

Left eye (March 1948)

Plate V Retinopathy of Undetermined Etiology Resembling Toxoplasmic Retinopathy

Right eye Case 14 Left eye

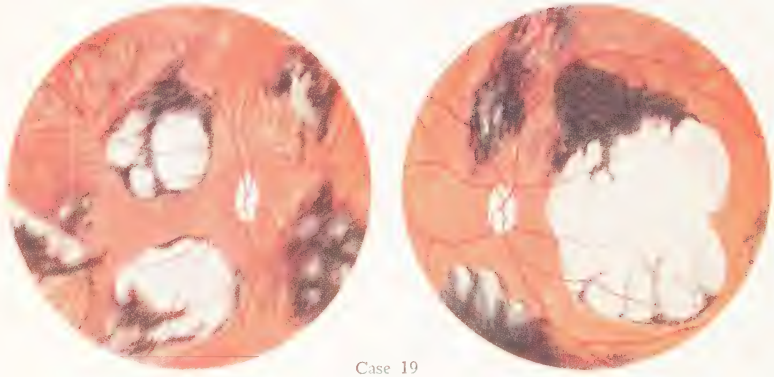


Right eye Case 15 Left eye

Right eye Case 16 Left eye

Plate VI Retinopathy of Undetermined Etiology Resembling Toxoplasmic Retinopathy

Right eye Case 17 Left eye



Right eye Case 19 Left eye

Right eye Case 20 Left eye

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